

AMERICAN JOURNAL OF OPHTHALMOLOGY

THIRD SERIES FOUNDED BY EDWARD JACKSON

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1. Gordon, D. M.: Scientific Exhibit, American Medical Association, Annual Meeting, San Francisco, 1958.



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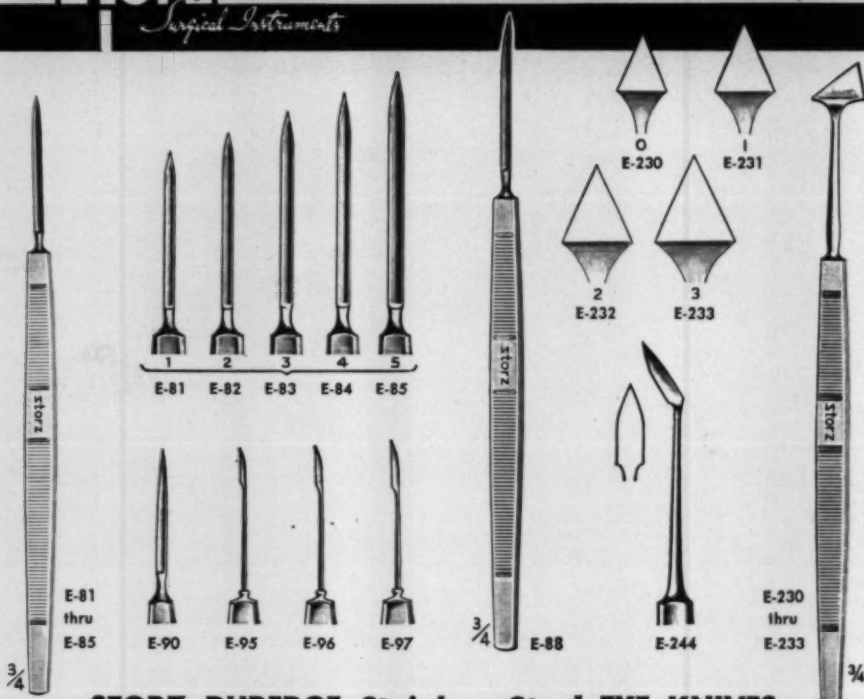
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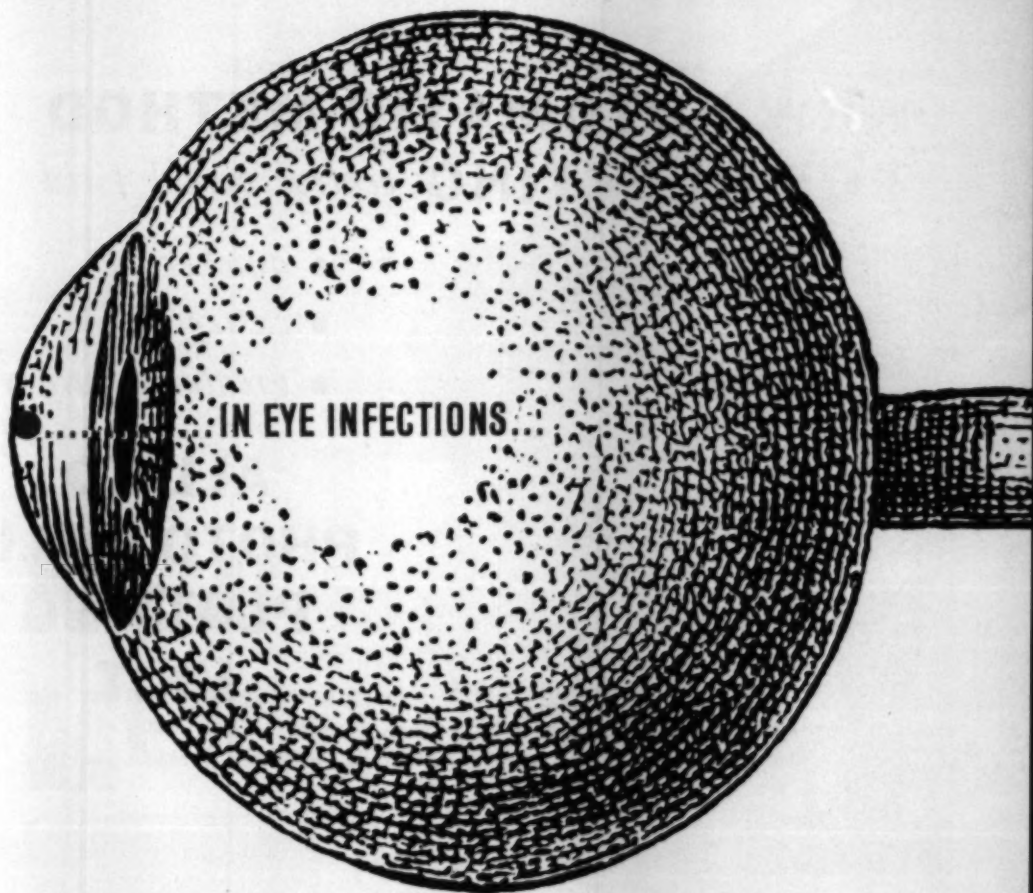
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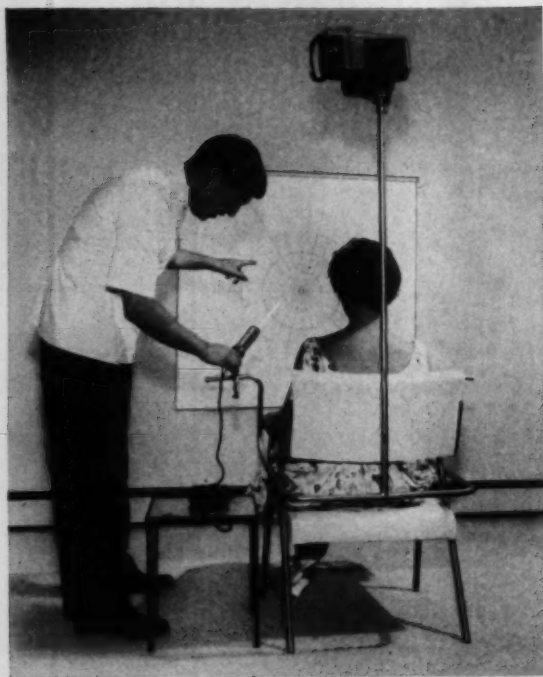
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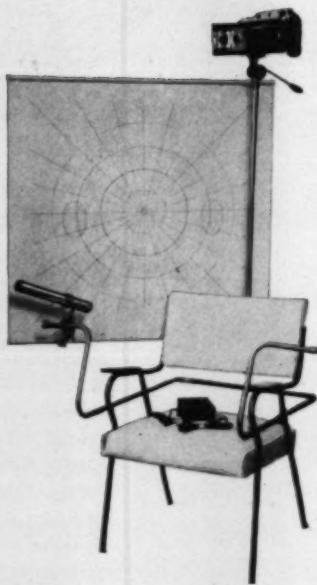
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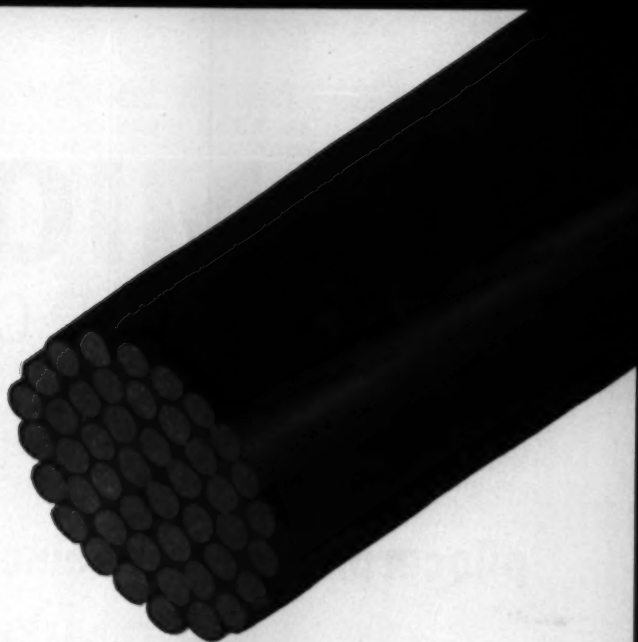


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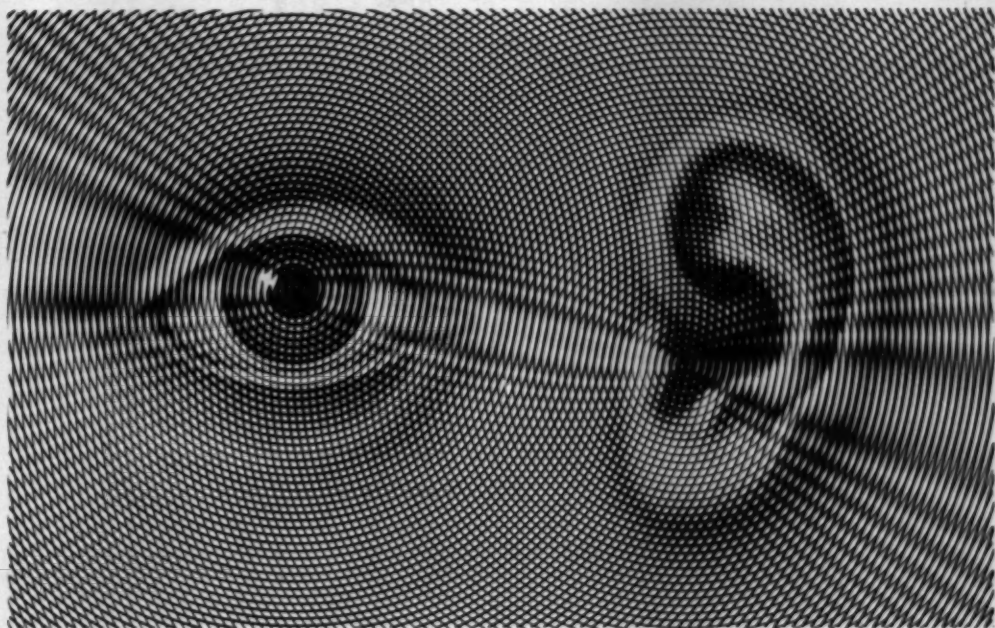
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*Witten, V. H.; Sulzberger, M. B., and Arthur, G. W.: *Clin. Pharmacol. & Therap.* 1:294 (May-June) 1960.



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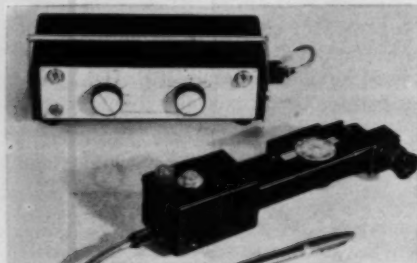
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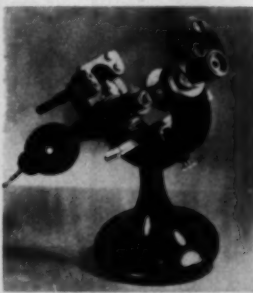
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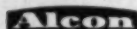
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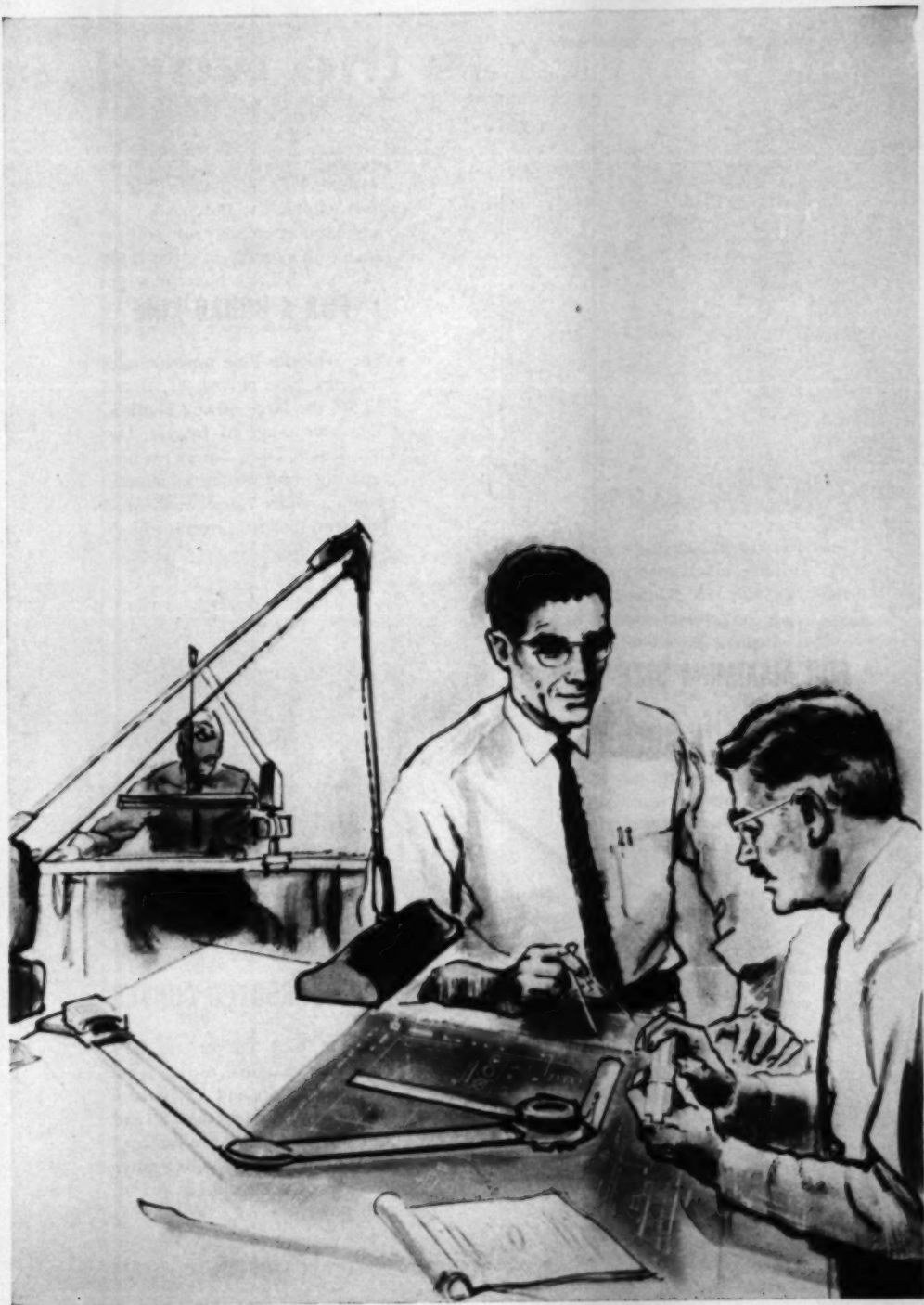
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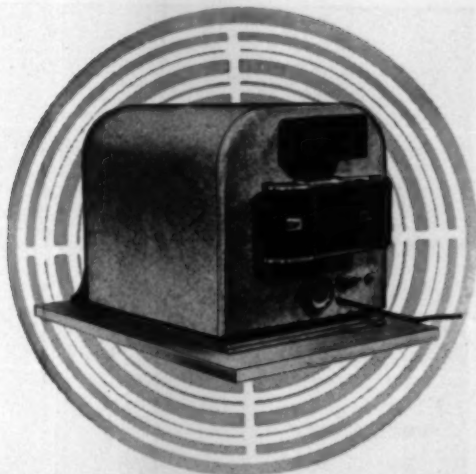
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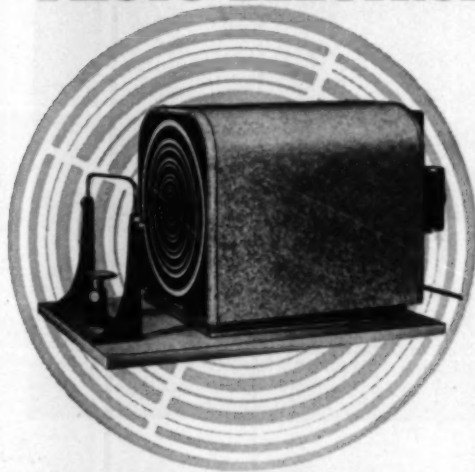
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1. *Am. J. Digest. Dis.* 22:5, 1955.
2. *Southwestern Med.* 40:120, 1959.
3. *Am. J. Ophth.* 42:771, 1956.
4. *M. Times* 84:741, 1956.
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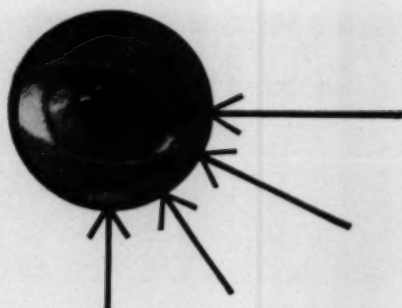
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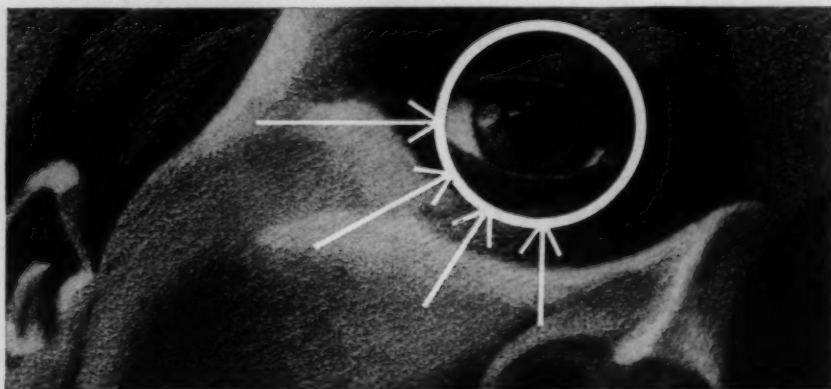
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1. Swan, K. C.: Tr. Am. Acad. Oph. 60:368, 1956.

2. Arora, R. B., et al.: E. E. N. T. Monthly 34:593, 1955.

3. Florestano, H. J., and Bahler, M. E.: J. Am. Pharm. A. (Scient. Ed.) 45:360, 1956.



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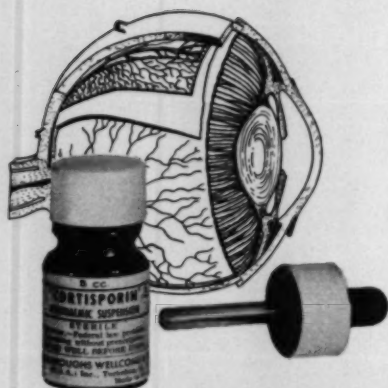
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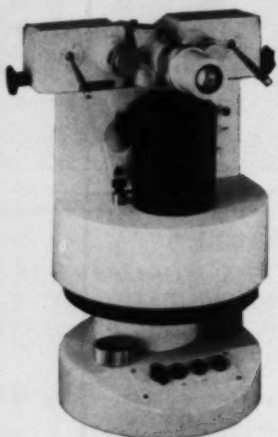
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The Francis Heed Adler Issue

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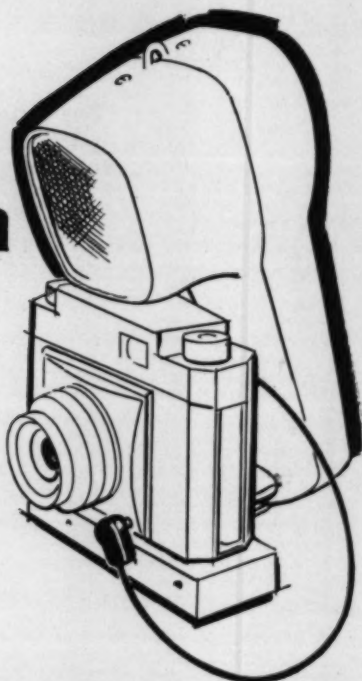
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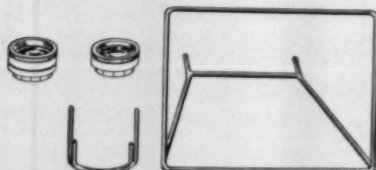
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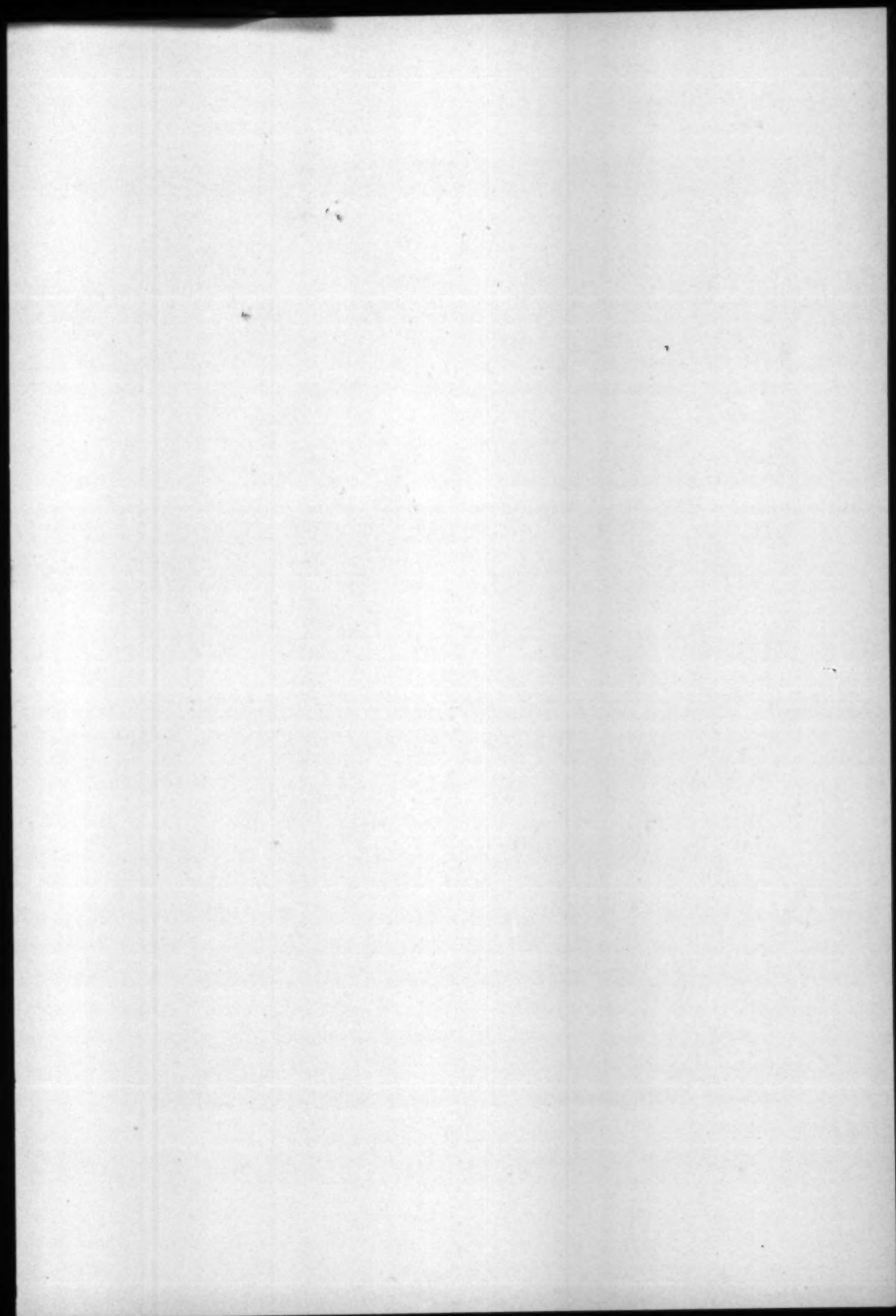


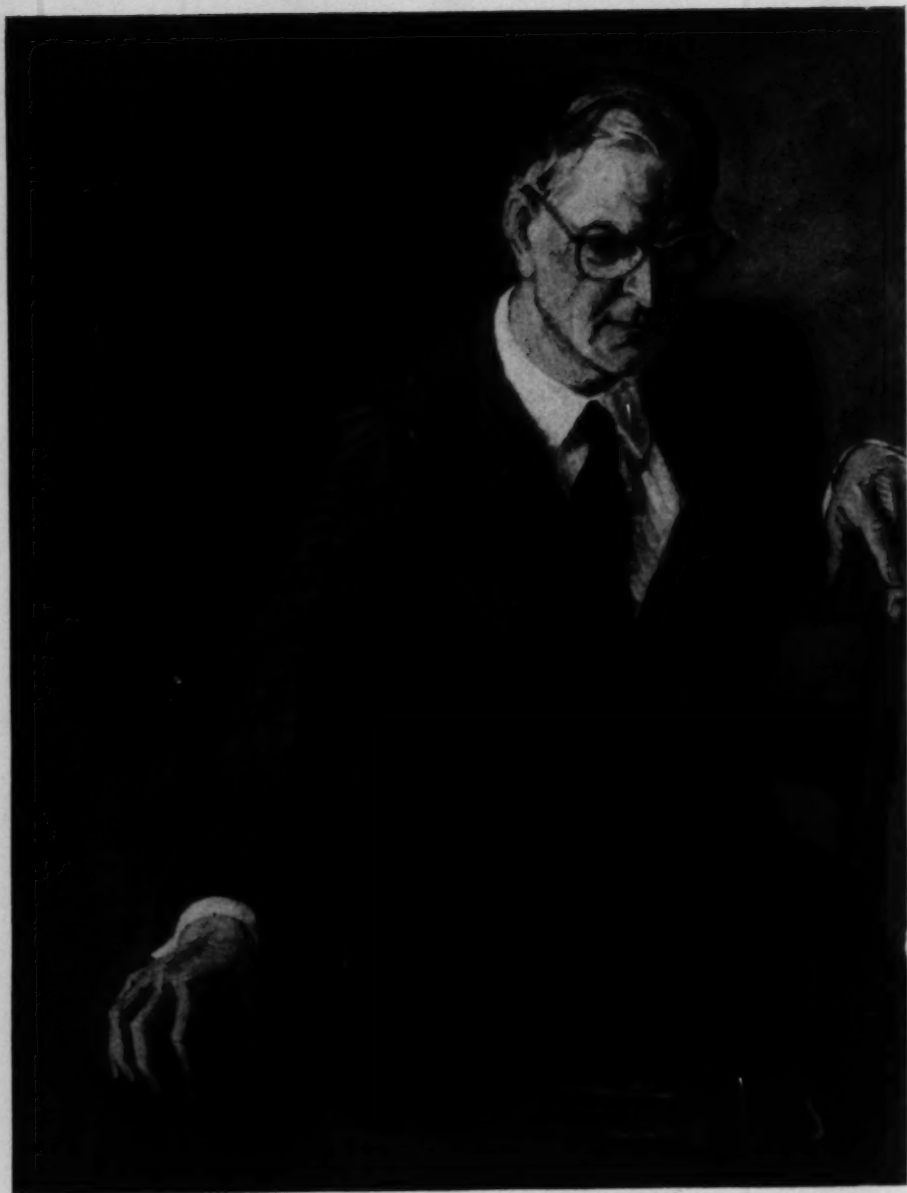
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FRANCIS HEED ADLER, M.D.

AMERICAN JOURNAL OF OPHTHALMOLOGY

VOLUME 50

DECEMBER, 1960

NUMBER 6

The Francis Heed Adler Issue

Francis Heed Adler, M.D., has distinguished himself in many roles during his lifetime of activity at the University of Pennsylvania, and his career has shed luster upon a community of admiring and distinguished colleagues.

As a student, he earned degrees in the College, the Graduate School of Arts and Sciences, and the School of Medicine. As a teacher, he became associated early in his career with the Department of Ophthalmology in the School of Medicine, and there he devoted himself for nearly four decades to enhancing medical education in his specialty. As a scholar, his pioneering in the application of findings in physiology to the study and treatment of ocular disorders has been reflected in a host of authoritative publications. As a surgeon, his eminence extends far beyond the confines of the University and its hospitals. As a medical administrator since 1937, he has developed within his department one of the finest clinical and academic traditions in the School of Medicine.

Professor Adler's many friends and colleagues from throughout the University join his confreres in medicine in acknowledging his myriad of contributions to the medical arts and to society at large. Together they wish him continued health and productive activity as he assumes Emeritus rank and confidently anticipate the maintenance of that inspirational companionship which has marked his distinguished career at the University.

Gaylord P. Harnwell
President
University of Pennsylvania

Former residents of the Hospital of the University of Pennsylvania who completed their training under Dr. Adler commissioned the artist, Franklin Watkins, to paint the portrait reproduced on the facing page.

SALUTATIONS

Dear Francis: Among the salutations in this volume dedicated to you none is written with greater warmth of affection than is this and few, if any, are based on longer and more intimate friendship.

I recall the enthusiasm and competence which marked your student years and particularly your discernment of the basic relationships of physiology with medicine. I recall the problem you began to study in my laboratory after your second student year and our disappointment on discovering that your color vision was such that you could not use the Duboscq colorimeter, an essential tool in the work. Could the discovery of that defect have had something to do with your later choice of ophthalmology as the field of your career?

In the 43 years which have elapsed since then you have, with unique singleness of purpose, become a true leader in your field—a teacher, the chief of a great hospital service,

a scientifically minded practitioner of the art of ophthalmology, and an incredibly productive author of works of lasting value. That professional singleness of purpose has not prevented the development of your artistic make-up through which you have invited your soul and delighted your friends.

The book in which you may perhaps read this tribute represents the beginning of a respite from long-obeyed obligations; by the same token it represents a new access of opportunity for the exercise of those cultural habits which, till now, could not find full expression.

I want these sentences to convey to you my sincerest congratulations on what you have made of yourself and on what, thereby, you have done for your profession, your patients, your school and hospital, and for the friends who love you. I am one of those.

A. N. Richards.

* * * *

It is a great pleasure to pay tribute to Dr. Francis Heed Adler. His accomplishments are manifold for he is both a scientist and a clinician; an author and an editor; a teacher and a scholar. In each of these categories he has excelled. His intimate knowledge of basic research and his great clinical experience combined with his clarity of thought and conciseness of expression have enabled him to portray in understandable terms the intricacies of ocular physiology. For his text on this subject he has won world-wide renown. As chief editor of the *AMA Archives of Ophthalmology* for 10 years he was superb. To this work he devoted himself unsparingly, for to him it was a labor of love. His keen intellect and his absorbing interest in both clinical and research ophthalmology found outlet in the demanding duties of this

assignment. As an editor he has been fearless yet sympathetic, exacting yet understanding, and critical yet eminently fair. All ophthalmology is indebted to him for the masterful manner in which he guided the destinies of this periodical through trying times and brought it to the pinnacle of success which it now enjoys.

It is ophthalmology's great loss that his tenure has ended for time is no barrier to the productivity of such a mind. To have served as a member of the editorial board of the *Archives of Ophthalmology* under the inspiring leadership of Dr. Adler was a privilege of which I shall always be proud.

John H. Dunnington, M.D.,
Member of Editorial Board
AMA Archives of Ophthalmology.

FRANCIS HEED ADLER, M.D.

The statistics of the life of Francis Heed Adler read somewhat like a Philadelphia story, while the impact of his life in the field of medicine and ophthalmology has been felt throughout the land and beyond. He was born on February 4, 1895, in Philadelphia, the son of Dr. Lewis H. Adler and Emma Augusta Heed Adler. His early schooling was at the Friend's Select School, until 1908, when he transferred to Blight's School, which was subsequently merged with Delancey School, from which he was graduated in 1912. After three years in the Department of Liberal Arts at the University of Pennsylvania, he entered the School of Medicine of the same University, and in 1916 received the degree of Bachelor of Arts. It was while still a medical student that his interest in physiology was first aroused, working under the guidance of Dr. Merckel Jacobs, both at the University and during the summer months in the Marine Biological Laboratory at Woods Hole, Massachusetts. Accordingly, he was awarded the degree of Master of Arts by the University of Pennsylvania in 1918, and one year later the degree of Doctor of Medicine, having attained the honor of membership in both Alpha Omega Alpha and Sigma Psi.

It was a natural step for him to take his intern years at the Hospital of the University of Pennsylvania, which in those days, of course, was for a two-year period, following which he embarked upon the double-barreled pursuit of both physiology and ophthalmology. In the former field, he was an instructor in physiology at the University of Pennsylvania for a 10-year period from 1922 to 1932, and an associate in physiology from 1932 to 1936. Simultaneously he was working as a member of Dr. deSchweinitz's staff in the Department of Ophthalmology of the Hospital of the University of Pennsylvania, and also became assistant surgeon in the clinic of Dr. B. F. Baer at the Wills Eye Hospital. From 1933 to 1937, he was attend-

ing surgeon at the Wills Eye Hospital, a position from which he resigned in 1937 when the call came from his alma mater to head-up the Department of Ophthalmology. It was characteristic of him to accept this position with enthusiasm, not only because of his loyalty to his University, but especially because of his devotion to the academic ideal, which he must have felt could be pursued to its greatest potential in the university atmosphere. While he was professor and head of the Department of Ophthalmology from 1937 until his retirement in 1960, his official title was changed, in 1945, to chairman of department, and William F. Norris and George E. deSchweinitz professor of ophthalmology, School of Medicine, University of Pennsylvania.

Many of Dr. Adler's early publications reflect his double interest in the fields of physiology and ophthalmology, as may be seen in the appended bibliography. This interest first reached its culmination in book form with the publication, in 1931, of his *Clinical Physiology of the Eye*, which for years was the only real treatise on this subject in the English language. Most of us are more familiar with his later book, *Physiology of the Eye: Clinical Application*, first published in 1950, and reaching its fourth edition in 1959. This effort has been far more than a rewriting of his original *Clinical Physiology of the Eye*, for, as stated in his preface to the first edition, "... the knowledge of this subject has so increased that an entirely new book, rather than a revision, is demanded." It is impossible to exaggerate the value of this text to students, practitioners, and teachers alike; and this book reflects the first great attribute of this man: his dedication to and tenacious interest in fundamental research, coupled with an uncanny ability to interpret the meaning of basic precepts in terms of practical clinical application.

Equally of value to another group of stu-

dents and physicians has been his series of revisions of *Gifford's Textbook of Ophthalmology*, first published in his revised form in 1948, and reaching its sixth edition in 1958. In addition to providing medical students and general practitioners of medicine with an authoritative and up-to-date source of the fundamentals in this field, this textbook reflects the second great attribute of this man: his enthusiasm and inspiration as a teacher. While he can prepare, as he did here, a fine textbook which can be understood by the uninitiated in ophthalmology; while he can deliver, better than most of us, a formal lecture in his field; while he can stand up at a meeting and discuss spontaneously a subject in which he is interested as though he had been up all night preparing it, he is far and away at his best, as all his residents have known, surrounded by six or 12 young men pursuing an idea, a thought, a principal; probing, searching, stimulating, guiding. This indeed is the true teacher; and while at times the resident has looked to others for the learning of a fact or even of a technique, he carries with him from this experience with Dr. Adler a critical and analytical approach which continues to permeate his thinking in ophthalmology throughout his professional life.

The residency program itself at the Hospital of the University of Pennsylvania was originated by Dr. Adler and developed by him with the aid in more recent years of his able associate and now successor, Dr. Harold G. Scheie. The clinical services include not only the University Hospital itself but also the Children's Hospital and the Veteran's Hospital, and most recently also the Philadelphia General Hospital. The residency has grown from a total of three to a total of 12 trainees, some 60 doctors now having completed their training under his tutelage. They have symbolized their high regard for their "chief" in commissioning Franklin Watkins to paint the portrait which is reproduced in this volume. This portrait was formally presented to the University

of Pennsylvania on April 7, 1960, by Dr. Adler's ex-residents. Characteristically, the "chief" has had copies in color made which he has presented to each of his ex-residents. We are all happy to have in our possession this typical pose of our teacher, apparently relaxed, but obvious to those who know him, poised and ready to spring in search of an idea.

This account would not be complete without mentioning some of Dr. Adler's other contributions to ophthalmology. He served for a number of years as a member of the American Board of Ophthalmology, and more recently as consultant to this board, pursuing his interest in proper testing procedures for candidates. He is a member of the American Ophthalmological Society and, in 1951, was awarded the Howe Medal by this society for distinctive service to ophthalmology. He is, of course, a member of the American Academy of Ophthalmology and Otolaryngology, and the American Medical Association, and served as chairman of the Section on Ophthalmology of the American Medical Association, the Medal of the Section on Ophthalmology having been awarded to him in 1959.

We are all aware of his long service with the *AMA Archives of Ophthalmology*, first as a member of the editorial board, and from 1949 to June, 1960, as the chief editor of this periodical. A continuous reader of that journal over the years will have observed and felt the touch of Dr. Adler's talents in the editorial field and will rejoice with Derrick Vail "that the superb editorial skills of Francis H. Adler will not be lost to ophthalmic literature" by his retirement. It was in this deservedly laudatory manner in which Dr. Vail announced Dr. Adler's acceptance of the position of consulting editor to *THE AMERICAN JOURNAL OF OPHTHALMOLOGY*.

As Dr. Vail further stated in this announcement about Francis Heed Adler, . . . "his talents and genius as a clinician, surgeon, editor, writer of textbooks, teacher and investigator in the clinic and the laboratory

are widely recognized and appreciated." We have touched upon some of the details of these attributes here, but how much more could be said! As stated during the presentation of his portrait to the University of Pennsylvania in April, 1960, . . . "while these many accomplishments are important, we can almost assume that they have been a part of the professional life of a man with this degree of intelligence, energy, and dedication. What can not be left out is a word about

the man himself; for, while he will be long remembered for his professional achievements, and while his burning interest in the academic phases of medicine and ophthalmology will be perpetuated by his more dedicated pupils, those of us who have worked with him and for him will particularly remember his kindness, his warmth, and his human faculty of being one of us."

William O. LaMotte, Jr.

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CONCERNING THE OPTIC CHIASM*

SELECTED PATHOLOGIC INVOLVEMENT AND CLINICAL PROBLEMS

THE DESCHWEINITZ LECTURE

FRANK B. WALSH, M.D., AND J. DONALD GASS, M.D.

Baltimore, Maryland

It is a high honor to be invited to give the deSchweinitz Lecture and I am grateful to you for the privilege accorded me. Distinguished colleagues who have preceded me on such occasions as this have established a high standard of excellence, and I approach my task with trepidation.

It would be unwarranted for me to undertake any eulogy regarding Dr. George E. deSchweinitz here in Philadelphia where some members of the audience have worked directly with him. I shall content myself by saying he will always be remembered as a great clinician, teacher and contributor. However, for my purpose this evening I wish to recall to you one of his greatest contributions which remains a milestone in neuro-ophthalmologic diagnosis. In 1923 he gave the Bowman Lecture, "Concerning certain ocular aspects of pituitary body disorders: Mainly exclusive of the usual central and peripheral hemianopic field defects."[†] In this paper he utilized the anatomic studies made by another famous Philadelphian, Dr. J. Parsons Schaeffer who was professor of anatomy of the Jefferson Medical College. This collabora-

tion originated in deSchweinitz' suggestion to Schaeffer: "that a restudy of the relational anatomy of the parts concerned might emphasize certain more or less established facts, and possibly bring some new factors to bear on the problem." This evening's paper concerns the intracranial area deSchweinitz studied intensively from the clinician's viewpoint. I like to think it would have interested him.

In the preparation of tonight's communication I received assistance from Dr. Donald Gass, and am pleased he has consented to be designated as co-author. Dr. Richard Lindenberg has supplied us with much material from his constantly expanding neuropathologic studies; his continuing co-operation is deeply appreciated.

Part I contains several figures exemplifying chiasmal involvements. No effort has been made toward completeness. Part II concerns some of the interesting problems we have encountered in the diagnosis of chiasmal involvement, and brief case reports have been included to exemplify the particular feature or features of interest. Also, attention is drawn to the occasional herniation of the gyrus rectus into the chiasmal cistern. The possible significance of such herniation is discussed briefly.

PART I. CHIASMAL INVOLVEMENTS PATHOLOGIC (figs. 1 to 11)

*From the Wilmer Institute of The Johns Hopkins University. Presented before the College of Physicians of Philadelphia, Section on Ophthalmology, November, 1960. This work was supported in part by grant 2110 (CI) of the National Institutes of Health, Public Health Service.

[†] II. The Bowman Lecture 1923. Tr. Ophth. Soc. U. Kingdom, 43:12-109, 1923.

(Part I, Figs. 1 to 11, follow on pages 1032-1038)
(Part II follows on pages 1039-1047)

PART I. CHIASMAL INVOLVEMENTS PATHOLOGIC (figs. 1 to 11)

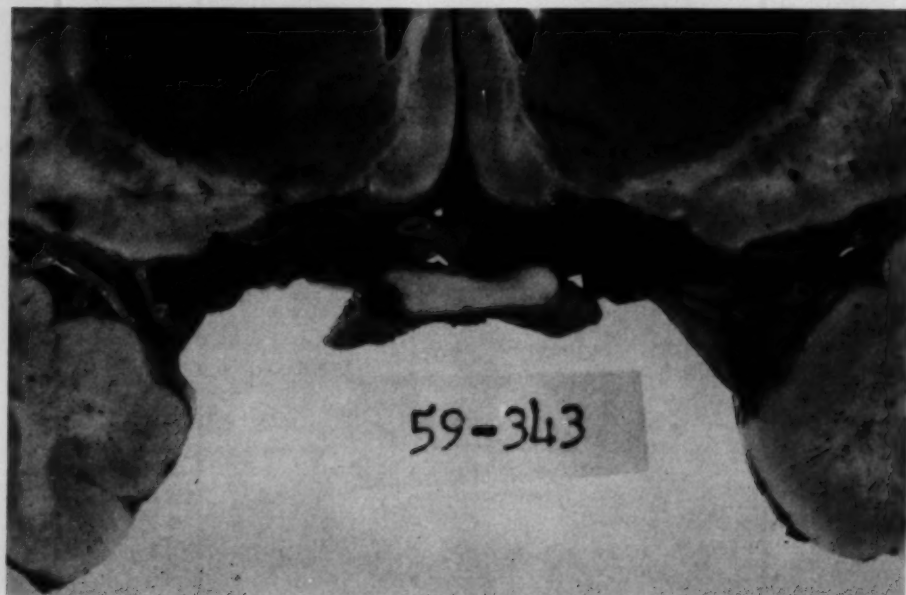


Fig. 1 (Walsh and Gass). Rupture of the chiasm. There was extensive fracture of the base of the skull.

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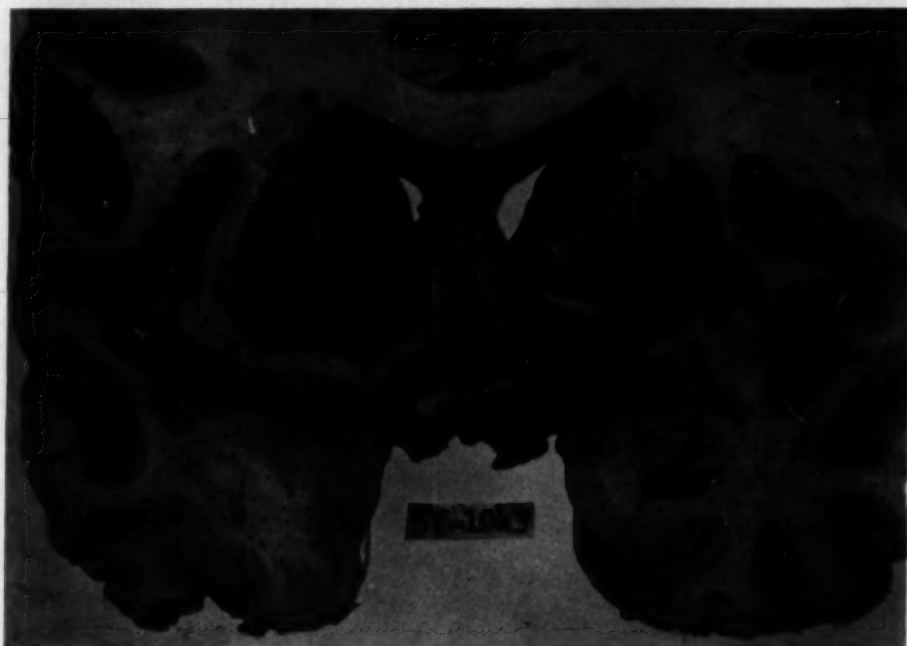


Fig. 3 (Walsh and Gass). Edema of the optic chiasm, with softening, hemorrhage of the pituitary stalk, and brain swelling. A. (707-57), a 34-year-old white man, was robbed and struck on the head. There was an extradural hematoma on the left. This was evacuated. He again became comatose and died 17 days after the injury. Death was attributed to aspiration pneumonia. Autopsy diagnosis: peritonitis due to perforated duodenal ulcer, mediastinitis due to esophageal ulcers complicating head injury. There was epidural hemorrhage over the vertex and numerous contusion hemorrhages in the hippocampal gyri and pituitary stalk. The optic chiasm was swollen and pressed against the sphenoid bone, thus the softening. Death occurred sufficiently soon after the injury that hydrocephalus had not developed.

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Fig. 2 (Walsh and Gass). Contusion of the chiasm with hemorrhage. J. (263-59) a man, aged 66 years, fell from the second floor of a porch and survived 16 days. He had frontal skull fracture extending through the right orbital roof for eight cm. He was bleeding from the right ear on admission to the hospital and was semicomatose. He never developed localizing signs. There was laceration of the right anterior orbital lobe, contusion hemorrhage of the left parieto-occipital region and the right frontal lobe superiorly, as well as contusion of the left lateral portion of the optic chiasm.

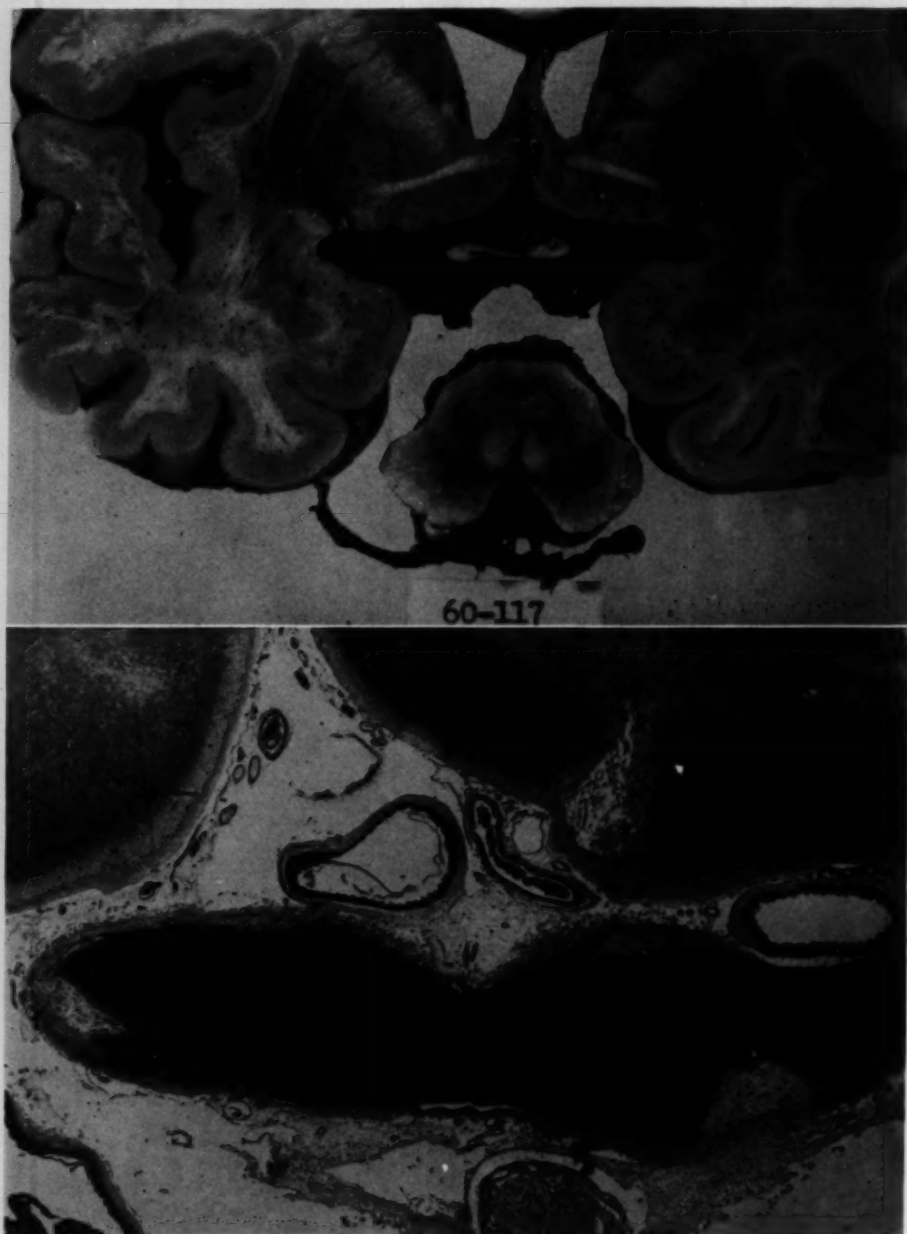


Fig. 4 (Walsh and Gass). Plaques in the chiasm in multiple sclerosis. D. (104-60) a white woman, aged 46 years, died of pulmonary embolism presumably secondary to phlebothrombosis of the right leg. Note the plaques in the chiasm, the areas of absence of myelin sheaths, and the glial scar formation. There were similar areas (in gray) about the third ventricle.



Fig. 5 (Walsh and Gass). Infrachiasmal aneurysm in a 43-year-old Negress who had been treated for heart trouble. Autopsy showed the presence of a subarachnoid hemorrhage from rupture of the aneurysm which is seen situated below the optic chiasm. It produced pressure on the inferior aspect of the chiasm and left optic nerve, more than right. Sections through the chiasm showed considerable atrophy.



Fig. 6 (Walsh and Gass). An unusual position (prolapse) of the anterior cerebral arteries which are pressing on the anterior chiasm and optic nerves. H. J. (61-58) a 64-year-old Negress, was fatally burned. Death occurred a few days later. Her history was unavailable but she was known to have been a long-time invalid. The anterior portion of the left temporal lobe has been removed so that the tortuous sclerotic middle cerebral artery can be visualized. There is pronounced atrophy of the left half of the midbrain (right). The dilated basilar artery is seen pressing on the third nerve. The optic tracts are seen at their commencement. Between the optic nerves and pressing into the chiasm are seen the dilated anterior cerebral arteries. This section has interest in regard to the herniation of the gyrus rectus. It is seen here that the anterior cerebral arteries may involve the same area.

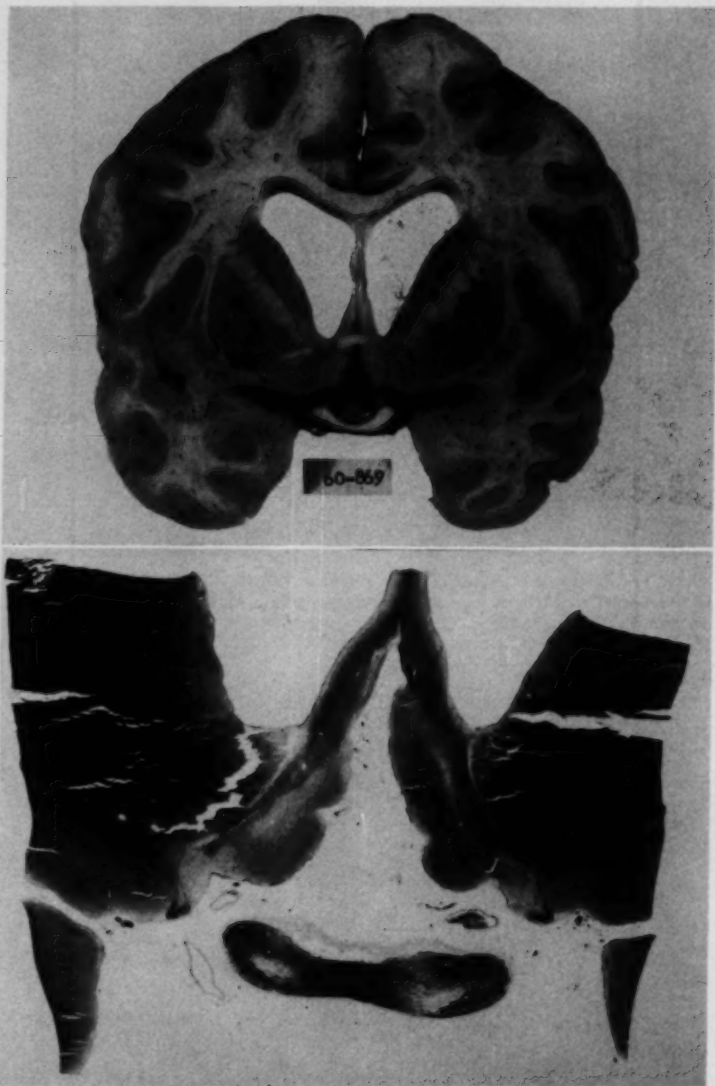


Fig. 7 (Walsh and Gass). Cerebellar tumor producing dilated third ventricle which is pressing on the chiasm. N. S. (548-60) a 27-year-old Negress, was found dead in bed. For two months she had complained of headaches. She was diagnosed as suffering from migraine and low blood pressure. (Above) Autopsy showed a cystic lesion of the left cerebellar hemisphere, herniation of the cerebellar tonsils, cerebral edema, and cystic glioma. There was obstruction at the fourth ventricle by the herniated cerebellar tonsils. There was medium dilatation of the lateral and third ventricles. (Below) Shows loss of myelin sheaths in the chiasm. The section is anterior to the region of the third ventricle. (Note that in some instances dilated ventricles result from atrophy of the cerebral cortex. This does not apply here. A dilated ventricle does not always indicate obstruction to the cerebrospinal flow.)

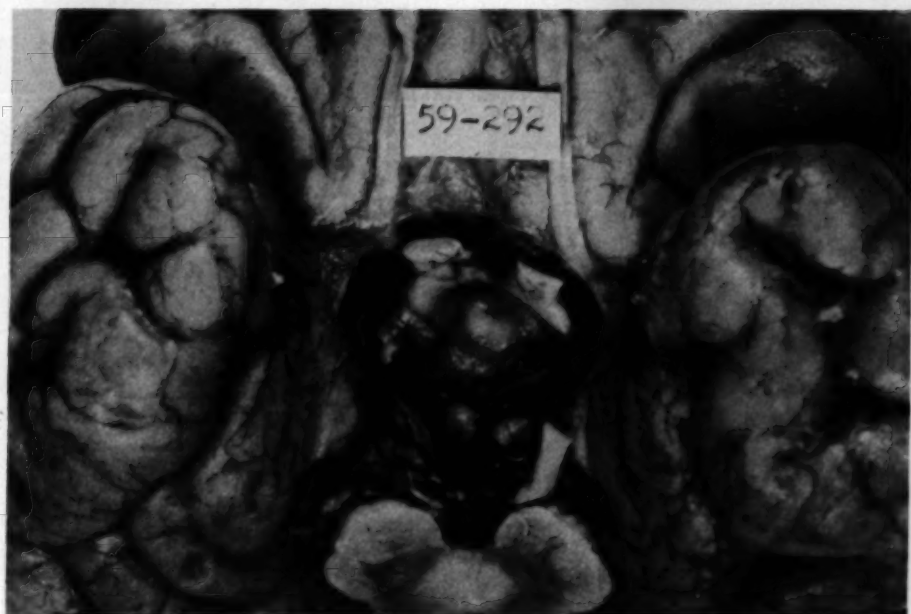


Fig 8 (Walsh and Gass). Pituitary adenoma found at autopsy in a woman, aged 71 years, who was found dead in bed. She had suffered from coronary thrombosis. It was said that at one time she had suffered from an external nasal condition but, so far as could be determined, there were no ocular complaints during life. There was streaklike gliosis in the middle of the optic chiasm.

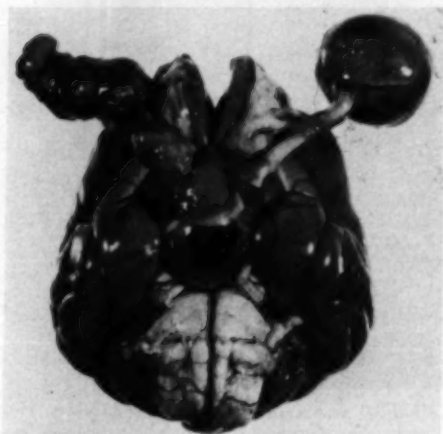


Fig 9 (Walsh and Gass). Spongioblastoma involving the right optic nerve and chiasm in a dachshund. The right eye had been enucleated. The dog was blind.



Fig. 10 (Walsh and Gass). Basilar meningitis.

H. M. (596-57) a 59-year-old Negro suffered from a self-inflicted gunshot wound. The point of entry was in front of the right ear, the exit in the left frontal region. An extensive debridement had been performed within a few days after the injury. After three weeks, he was admitted to The Johns Hopkins Hospital, unconscious and with an elevated temperature. Pus was exuding from the left frontal wound. A further debridement was performed. Death occurred after several hours. The appearance of the frontal lobes is, in part, the result of the debridement. Such an extensive basilar meningitis, had recovery been made, could have accounted for optic nerve damage and cranial nerve palsies.

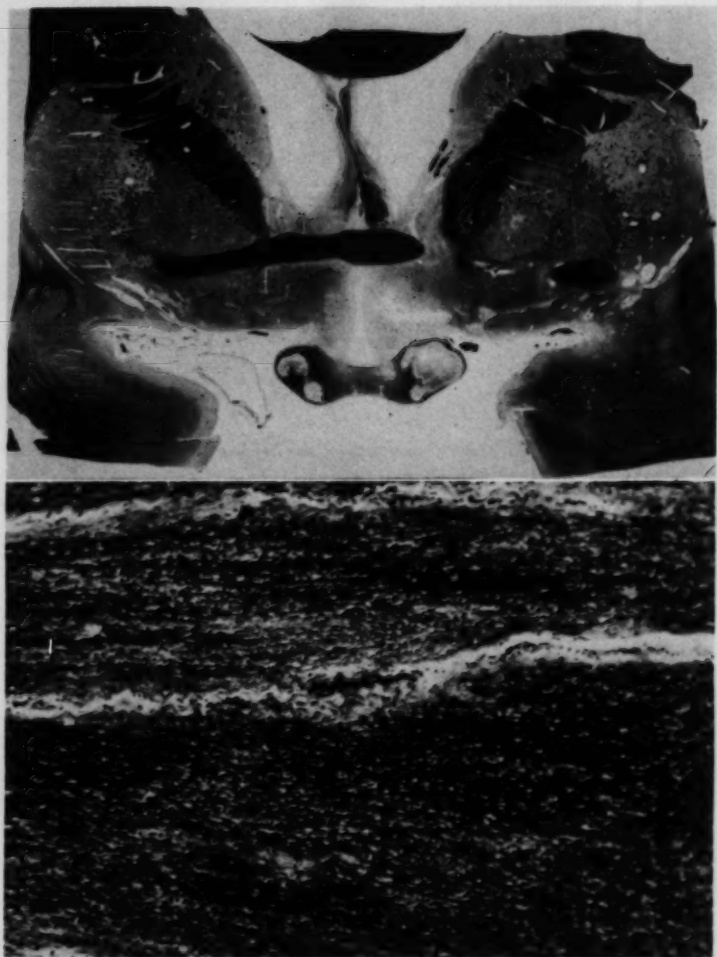


Fig. 11 (Walsh and Gass). Insulin poisoning. R. C. (426-59) was a diabetic man, aged 43 years. He was given a diet and 15 units of insulin daily. One evening he returned to his home intoxicated. He injected 240 units of insulin, collapsed and became comatose. He survived for 11 days but remained in a shocklike state. Death was attributed to bronchopneumonia. There was extensive congestion and necrosis of the cerebral cortex (the anterior central and calcarine areas were better preserved than the other cortex; not shown). There was pronounced swelling of the chiasm, with areas of softening (above). (Below) Areas of softening are shown in the chiasm (myelin sheath stain).

PART II. CHIASMAL INVOLVEMENTS, CLINICAL

1. WHEN LOSS OF TEMPORAL FIELD IS UNILATERAL

Recently two patients have complained of unilateral visual field loss, and in both instances the left temporal field was defective.

Case 1. B. S. (94-77-55) a white woman, 45 years of age, described a scratching sensation in the left eye present for three months, and loss of vision in that eye for one month. She had observed that the field loss was in the temporal field. There was no complaint of pain in the eye or elsewhere. Hearing had been defective for years. X-ray films of the skull, including the optic nerves and sinuses, gave normal findings, and chest X-ray films were normal.

The eyes were normal externally. Vision was: R.E., 20/20 with a small myopic correction; L.E., 10/200, with -1.75D. sph. \ominus -0.25D. cyl. ax. 70°, 20/70. With a 1.25D. add 0.5M, R.E., 1.25M, L.E. The right optic fundus appeared normal. The left optic disc was pale. Slitlamp examination gave normal findings. Ophthalmodynamometer readings, diastolic 30 for each eye. The visual fields are shown in Figure 12. Repeated examinations of the right visual fields were required to satisfy us that there was a defect in the temporal field.

A left carotid arteriogram showed a suspicious lifting of the anterior cerebral artery.

At operation a suprasellar meningioma arising from the tuberculum sellae was removed. Four days

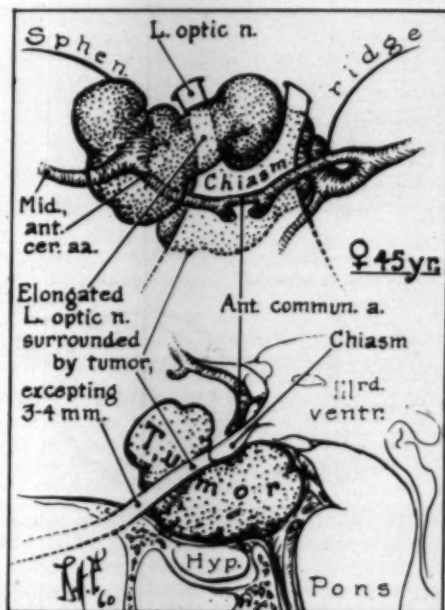


Fig. 13 (Walsh and Gass). Case 1. Diagram illustrating extent of meningioma (Padgett).

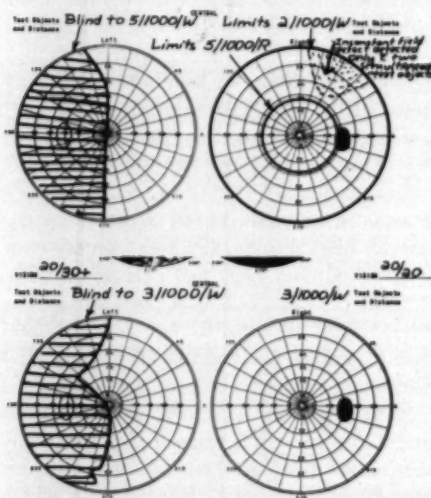


Fig. 12 (Walsh and Gass). Case 1. Fields before and after operation. There was great difficulty in deciding that there was a field defect in the right eye.

after operation the visual acuity of the left eye had improved to 20/30 and it so remained until her discharge to her home. At the present time the patient has not been re-examined (fig. 13).

Case 2. V. D. (96-61-23), a white woman, 47 years of age, about six months before our examinations observed that when she covered her right eye the temporal field of the left eye was defective. She had no other complaints. She had always been healthy. Her menstrual periods had stopped when she was 42 years of age.

The eyes were normal externally. Visual acuity was 15/20 corrected to 20/20 and 0.5M for the right eye, and 15/30 not improved, 0.75M for the left eye. The right optic fundus appeared normal. The left optic disc was slightly pale. Slitlamp examination was not remarkable. The visual fields are shown in Figure 14.

X-rays of the skull showed expansion of the sella turcica with erosion of its floor and some erosion of the posterior clinoids.

At operation the pituitary tumor was found to be in large part a cyst. Operation has been done two weeks past at the time of writing and recovery so far has been uneventful.

COMMENT. Two features of Cases 1 and 2 are commented upon: the visual fields; the

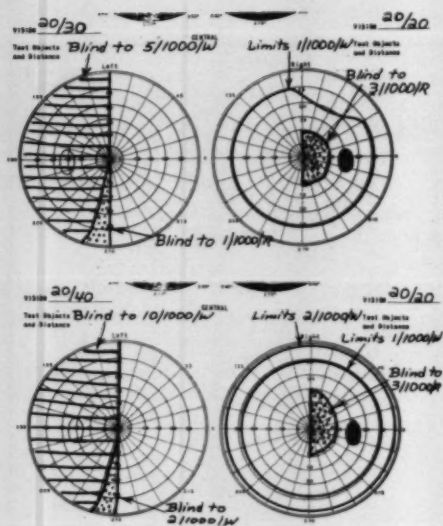


Fig. 14 (Walsh and Gass). Case 2. Fields before and after operation.

lack of direct relationship between the extent of the tumor and the loss of function as observed in Case 1.

Lesions which primarily involve the chiasm produce bitemporal field defects, and such defects may be dissimilar for the two eyes. Identification of minimal temporal field loss in the opposite eye is the interesting feature under consideration here. It may be difficult to determine, as exemplified in Case 1.

When hemianopic features are definite in one temporal field it would be anticipated that with a chiasmal involvement there must be a temporal defect in the field of the opposite eye. In occasional instances such as this it may remain undetected until carefully looked for and rarely it may not be present. When the field defect in the opposite eye is paracentral, the use of colored test objects (red) facilitates recognition of the defect in many instances, according to our experience; this is exemplified in Case 2.

Further, as regards the extensive unilateral field defects in both Case 1 and Case 2, the diagnosis of optic neuritis had been suggested. We have observed unilateral optic

neuritis which accounted for extensive loss of lower and less often of the upper visual field with or without good central visual acuity, but such extensive loss has not involved only lateral fields, temporal or nasal, according to our experience.

The tumor removed at operation (Case 1, fig. 13) well might have produced more extensive loss of vision and fields than it did. In some instances extensive involvement by tumor produces little functional loss, whereas in other instances, a small tumor accounts for pronounced functional loss. This, of course, is generally well known but has seemed to deserve retelling. We have observed a third nerve completely surrounded by meningioma when no abnormality of ocular movements could be detected and when there had been no complaint of double vision.

2. WHEN THERE IS ACUTE VISUAL FAILURE

Lesions which involve the anterior visual pathways in many instances are responsible for rapid loss of vision. Uihlein and Rucker* reviewed experiences in the Mayo Clinic concerning such occurrences and listed the various conditions they found to be responsible in the order of frequency with which they were encountered: (1) pituitary tumor, (2) tumor of the optic nerve or chiasm, (3) supraclinoid aneurysm, (4) parasellar lesion, (5) thrombosis of the carotid artery, (6) hydrocephalus of the third ventricle, (7) chiasmal arachnoiditis, (8) fracture of the anterior cranial fossa, (9) basofrontal tumor of the skull, and (10) pseudotumor cerebri. We have not surveyed our experiences in The Johns Hopkins Hospital but feel it would closely parallel the findings of Uihlein and Rucker.

Here attention is drawn to sudden bilateral loss of vision when it is preceded by pain in the head and is associated with bilateral ophthalmoplegia. In cases with which we are familiar, the patient has suffered from hemorrhage into a pituitary adenoma,

* Arch. Ophth., 60:223-229, 1958.

or infarction of such a tumor, accounting for sudden swelling of the pituitary. In what we visualize as the classic syndrome there has been (1) pain in the head, (2) loss of vision which tends to be bilateral and if incomplete is associated with bitemporal field loss, and (3) ophthalmoplegia which tends to be bilateral and pronounced.

Case 3. J. B. A. (24-67-33) an acromegalic, after experiencing severe headaches developed overnight a total external ophthalmoplegia and gross loss of temporal visual fields. Operation revealed a swollen pituitary with tumor but without hemorrhage. There was rapid recovery from the ophthalmoplegia and the field defects disappeared.

3. WHEN THE HISTORY OF SYSTEMIC DISEASE CONFUSES THE DIAGNOSIS

The history summarized in Case 4 has intrinsic interest and possible value as regards co-operative efforts in diagnosis.

Case 4. K. M. (91-77-81) a 42-year-old white woman was examined in July, 1960, because of defective vision in both eyes present for three months. The loss of vision was from the first more severe for the left eye, was described as rapidly progressive and unassociated with other symptomatology. The eyes were normal externally. Vision was: R.E., 10/200; L.E., perception of hand movements at eight inches. The visual fields are shown in Figure 15.

Ophthalmoscopic examination showed the right eye to have clear media. The optic disc was yellowish in color. The macula appeared normal. The peripheral fundus had a granular appearance with scattered spots of pigment in the far periphery, with the pigment possibly principally accumulated near vessels. The retinal arteries and veins were definitely narrowed as compared with the vessels of the left eye but the narrowing was not extreme. The optic fundus on the left, including the optic disc, appeared within normal limits, excepting the far periphery where the appearance was similar to that of the right eye. What was seen with the ophthalmoscope could not explain the pronounced loss of vision and visual fields. Slitlamp examination gave normal findings.

PAST HISTORY. In 1939 the patient was working in a restaurant and a blood test for syphilis was positive. She denied genital or skin lesions. Serologic tests on the blood were positive on several occasions from 1939 to 1943, during which period she was given routine antisyphilitic treatment. Spinal fluid examination in 1942 gave negative findings; other such tests if made were not recorded.

In May, 1960, during a hospital admission to relieve recurrent dislocation of the shoulder, she was given penicillin postoperatively for five days.

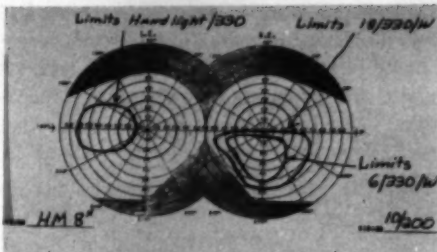


Fig. 15 (Walsh and Gass). Visual fields for patient K. M. (Case 4).

This was about the time she first noted loss of vision but there was no notation regarding such a complaint and her eyes were not examined.

THE JULY ADMISSION (continued). Physical examinations gave entirely normal findings excepting for the eyes. The cerebrospinal fluid was normal in all regards. There was a weakly positive cardiolipin flocculation test on the blood. X-ray films of the skull were read as normal. It was decided that left carotid arteriography was not necessary and that exploration was unnecessary.

A right carotid arteriogram was made. The anterior cerebral artery was thought to be bowed forward slightly but all the vessels that filled were tortuous; there was good cross-filling. A pneumoencephalogram was read as normal. It was decided that left carotid arteriography was not necessary and that exploration was unnecessary.

Our problem concerned correlation between the ophthalmoscopic appearance and the extensive visual loss in an individual who had serologic evidence of syphilis. I was reasonably certain that syphilis was not responsible and accepted the evidence obtained by arteriography and encephalography. The patient was given two courses of penicillin and discharged from hospital, with instructions to return for further observation.

SUBSEQUENT COURSE. Approximately three weeks after discharge the patient was admitted to hospital in another state. On arrival she was in extremis. The pupils were dilated and fixed, she was areflexic and in respiratory distress. There was severe bilateral papilledema. After intubation it was possible to do several examinations. Ventricular tap yielded bloody fluid. Arteriography revealed a large (English walnut size) aneurysm in the left internal carotid artery. At autopsy the aneurysm was seen to arise from the carotid artery and from its position it produced pressure on the optic chiasm; it had ruptured superiorly into the third ventricle. The aneurysm was studied histologically and was of the congenital type. This information was obtained through Dr. Frank B. O'Connell, Jr., and Dr. John Chambers.

COMMENT. Our failure to establish the diagnosis in this case points to a vital consideration as regards collaborative studies.

One examiner must take the responsibility for the final analysis. In this instance we should have requested a left carotid arteriogram, and exploration if it appeared negative. There is no doubt in our minds that such procedures would have been undertaken.

4. OPTICOCIASMATIC ARACHNOIDITIS

Mention is made here of this affection only because its existence as a specific and spontaneous development was for many years questioned in The Johns Hopkins Hospital. We have observed two patients, both of whom exhibited paracentral bitemporal field defects, and in whom this diagnosis was established beyond reasonable doubt. Recovery followed operation. These cases have been reported elsewhere. We have not encountered any example of central scotomas resulting from opticochiasmatic arachnoiditis.

5. CENTRAL SCOTOMAS AND CHIASMAL INVOLVEMENTS

We have observed a combination of a central scotoma in one visual field and on associated temporal defect in the field of the opposite eye with suprasellar tumor. Also we have found a unilateral central field defect in proven pituitary tumor when the field for the opposite eye seemed normal. The occurrence of bilateral central scotomas in association with pituitary tumor has been observed in a single instance.

6. WHEN TUMORS OF DIFFERENT TYPES ARE PRESENT IN ONE INDIVIDUAL

Multiple intracranial tumors are occasionally encountered, and we have observed such cases. We have selected for your consideration a case in which confusion as regards the etiology of bitemporal field defects persisted until a second tumor was discovered at operation.

Case 5. E. K. (83-60-02) a 50-year-old white woman, approximately 15 months before our first examinations, observed that she had defective vision

in the left eye. Some three months later it was discovered that she had bitemporal field defects and she was ultimately referred for diagnosis and treatment.

PAST AND FAMILY HISTORY were unimportant as regards her defective vision.

EXTERNAL EXAMINATION of the eyes gave normal findings. With correction for moderate hypermetropia the visual acuity was 20/50 for each eye, and 20/25 when both eyes were used together. With an appropriate add she read small print slowly, each eye. Fields showed bitemporal loss. The optic fundi seemed normal. X-ray films of the skull gave normal findings. A left carotid arteriogram showed elevation of the middle cerebral complex on that side but no tumor stain was present. The arteriogram suggested a laterally placed tumor possibly a meningioma on the sphenoid ridge but no evidence of a suprasellar tumor.

The findings on arteriography did not explain the visual field defects. It was suggested there might be extension of a sphenoid ridge tumor to the midline. The possibility that two tumors were present was considered and that one might be found above the sella. A pneumoencephalogram showed impingement on the temporal horn of the left lateral ventricle, which was compatible with the arteriogram. There was a question of the normalcy of the suprasellar area in the encephalogram but it was uncertain, and this area would be visualized at operation.

Following the air study a craniotomy was performed (Dr. John Chambers). A left sphenoidal wing meningioma was removed in toto. This tumor had extended to within five mm. of the left optic nerve. The chiasm and the optic nerves were well visualized and were thought to appear quite normal. Because the bitemporal field defects suggested the possibility of a suprachiasmatic tumor, Dr. A. Earl Walker was asked to look at the area in question and he agreed that it appeared normal.

After the operation the patient did well for 24 hours and then became obtunded. The right pupil became dilated and fixed to light; the pulse rate fell to 60 per minute and there were short periods of apnea. She was again taken to the operating room and the wound was opened. No significant clot was found and there was no evidence of increased intracranial pressure.

EKGs, were normal; serum calcium, phosphorus, and potassium were normal. The pupils returned to normal and she seemed better with, however, some motor aphasia. Next she developed a third-nerve palsy on the right but this was transient.

Within the postoperative period of 30 days after the last procedure, she gradually improved and became oriented. She was able to read the daily paper when she was discharged from hospital. The bitemporal field defects remained unchanged. There was slightly increased fluid intake and output. An explanation for the bitemporal hemianopia was still wanting.

Five months later the patient was readmitted because of having developed a bluish fluctuant mass

two by five cm. in area on the frontal portion of the scalp in the midline. A thrill was palpable. The mass was easily compressed. A bruit could be heard. The thrill and bruit were greatly diminished with pressure over both superficial temporal arteries.

The patient was apathetic, poorly oriented, and co-operation was such that examination of the eyes was unsatisfactory. It was concluded that they were normal externally and that there was some remaining nasal field for the right eye. Sensation was intact. Motor power was equal bilaterally and posture and gait were normal. There were no cerebellar signs. Superficial and deep tendon reflexes were present and equal.

The impression was: arteriovenous fistula in the scalp near the point of the old craniotomy scar; incontinence of urine; changes in sensorium compatible with frontal lobe damage. The vessels feeding the arteriovenous fistula in the right frontal region were ligated. The postoperative course following this was stormy with difficulty with respirations. She became completely confused and disoriented. Six days after the ligation of vessels the bruit which had disappeared again became audible.

Bilateral carotid arteriograms were made but showed nothing remarkable. An air injection showed a dilated left ventricle with a shift to the right. A Torkildsen procedure was performed. Finally, a third craniotomy was undertaken. It revealed a craniopharyngioma in the suprasellar and chiasmal region. The patient died.

COMMENT. There are several remarkable features in this case.

The examination procedures made on the patient's first admission gave results compatible with what was found at operation only in part. An explanation for the bitemporal hemianopia was not found and the entire chiasmal region had been exposed to view and been considered normal. Subsequently a suprasellar craniopharyngioma was found to extend posteriorly to involve the thalamic region.

Could there have been rupture of a cyst when the first operation was done? Was the tumor intrasellar at the time of the first operation? Of course, the most likely explanation is that, after the first operation was done, the tumor had extended forward. Even so it remains remarkable that it could not be recognized when first viewed. (The remarkable arteriovenous fistula is to be described by Dr. Chambers in a separate communication.)

7. WHEN BITEMPORAL FIELD DEFECTS ORIGINATE IN LESIONS FAR DISTANCE FROM THE CHIASM

Bitemporal hemianopia indicates involvement of the chiasm in a majority of cases. In most instances the primary lesion is responsible for the field defects. However, occasionally such field defects originate in lesions far distant from the chiasm. In such an instance the bitemporal field defects have a false localizing value as regards the primary lesion. With tumor in the posterior fossa the mechanism is generally well known. There may be obstruction to the circulation of cerebrospinal fluid and dilatation of the third ventricle which through pressure may account for chiasmal involvement. In such cases the correct diagnosis frequently is delayed, particularly when the evidence for posterior fossa involvement is minimal. We have recently observed an individual who exemplified what is being considered here. Only the pertinent features of the case are recounted.

Case 6. A. F. (91-34-63) a white woman, aged 20 years, complained of failing vision for eight months prior to our examinations. Twelve months earlier she had commenced complaining of headaches which were situated posteriorly and in the neck. These headaches continued irregularly to the time of our examinations when she described only a sense of discomfort in the posterior head and in the neck. She had dizzy spells which were said to have been associated with weakness of the right hand, arm and leg; these lasted for as long as a day or two during which time she was unable to get about. She was vague about the frequency of these episodes and it could only be concluded that she had had several such occurrences. It was observed by her friends that, during the episodes, she was red-faced and her breathing was rapid after the spell had commenced.

When she was five years old a needle had penetrated her right eye and the vision in that eye subsequently was defective. In consequence, her complaints principally concerned her left eye. She described the vision during eight months as fluctuating but generally progressively worse. There were no complaints of pain, halos, and so forth. She had been suspected of having disseminated sclerosis.

PAST HEALTH. She had had frequent ear infections and the hearing on the left was diminished. Infected teeth had been extracted just prior to her admission here. She gave a history of "hives" when exposed to cold. She had been told she suffered

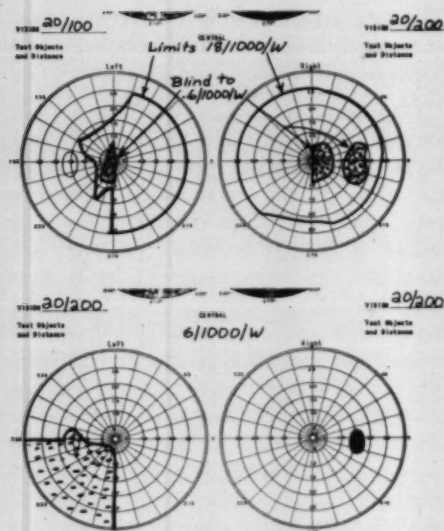


Fig. 16 (Walsh and Gass). Case 6. Fields before and after operation. Central field defects were not plotted but must be present.

from sinusitis. At 16 years of age she weighed 250 pounds but during four years dietary discretion had accounted for a loss of weight of approximately 100 pounds.

FAMILY HISTORY. Her mother, at the age of 43 years, developed paraplegia and unilateral facial palsy. The diagnosis was multiple sclerosis but three years later she was found to be quite normal. She was not seen by us.

EYE EXAMINATION. The eyes were normal externally excepting as regards the right pupil which was irregular and drawn down toward the 7-o'clock position. Optokinetic responses were normal in the horizontal positions. Visual acuity was 20/200 and 20/100, read M1.00 for the right and left eyes respectively, and could not be improved. The media of the right eye were clear. The optic disc was slightly elevated and had slight neovascularizations on it and it was definitely pale; the macula was granular; the veins were tortuous and the arteries possibly a trifle narrow. The left eye was similar to the right with more neovascularization on the optic disc. The visual fields contained bitemporal defects (fig. 16).

PRELIMINARY IMPRESSION. The appearance of the optic discs was compatible with optic neuritis or ancient papilledema. There was no obvious evidence of involvement of the nervous system other than the eyes, excepting for some conduction deafness on the left and a questionable Romberg sign. At this time the possibility of a suprasellar tumor was considered.

Ear, nose and throat examination revealed middle ear damage on the left. X-ray films of the

mastoid showed sclerosis on the left. It was then suggested she had cholesteatoma.

NEUROLOGIC EXAMINATION revealed minimal defects except for the eyes. Romberg's sign was not present. The deep tendon reflexes were more active on the right than on the left; there was decreased swinging of the right arm during walking; minimal right facial weakness; slight unsteadiness of the right arm. Two-point discrimination was slightly more accurate on the right than on the left hand.

A left carotid arteriogram showed widening of the normal curve of the anterior cerebral artery on the lateral film. This suggested a dilated lateral ventricle. A right vertebral arteriogram suggested compression of the basilar artery resulting in partial failure in filling of the posterior cerebral arteries. An air study showed marked hydrocephalus and slight deviation of the aqueduct to the right.

OPERATION. A cyst with mural nodule was removed from the left cerebellar hemisphere. A course of X-ray therapy was administered before the patient was discharged from the hospital.

COMMENT. A patient, aged 20 years, was admitted with a suggested diagnosis of disseminated sclerosis. Because of the changes in the visual fields it seemed she might suffer from a suprachiasmatic tumor. The procedures leading to the proper diagnosis of cerebellar tumor have been outlined.

In such cases as this the optic chiasm is involved through pressure of the distended third ventricle (fig. 7).

8. HERNIATION OF THE GYRUS RECTUS

It is generally well known that distension of the third ventricle may account for involvement of the optic chiasm and optic nerves as exemplified by Case 6. Also it is known that adjacent parts of the brain may press upon the chiasm or optic nerves. However, herniation of the gyrus rectus insofar as we are aware has not been described as an entity responsible for ocular signs. We have evidence suggesting that such herniation, unilateral or bilateral, may be significant in this regard but more studies are required.

Case 7. G. C. (UM Path 64394), a 40-year-old white man, was admitted to the hospital in 1955 with a history of headaches for several years, and drowsiness, mental slowness and urinary incontinence for about six months. Examinations revealed pronounced papilledema bilaterally and slight weakness of the left arm. X-ray studies gave normal findings. A ventriculogram suggested the presence



Fig. 17 (Walsh and Gass). Herniation of the gyrus rectus (Case 7). G. C. (59-206). (Above) The herniation is more severe on the right. There is increased angulation of the chiasm. (Below) Note thinning of the bone, particularly in the left. The optic nerve can be seen through the bone. The entire bony base is thinned from pressure. There was diffuse loss of myelin sheaths in the intracranial optic nerve, as well as in the chiasm (sections not shown).

of a large bifrontal mass in the posterior frontal region. A right frontal craniotomy was performed. A large bifrontal meningioma arising from the falx was removed (weight 150 gm.). The patient was discharged from the hospital greatly improved.

Four months after discharge he consulted Dr. Richard Hoover, complaining that his glasses were unsatisfactory. The eyes were normal externally. Visual acuity with a low-grade hyperopic correction was 20/25, O.U., read 0.5M each eye. The disc margins were slightly blurred and the discs were pale with deep cupping but no suggestion of glaucoma. Ocular tension was normal for each eye. Repeated efforts were made to chart the visual fields but this could not be done with an accuracy. However, Dr. Hoover was completely sure that a bitemporal field defect was present.

In 1959 the patient died as a result of coronary occlusion and an autopsy was performed. The studies (fig. 17) made by Dr. Lindenberg are of interest particularly in regard to the bitemporal field defects.

Case 8. M. M. (CR 60-26. U. M. 20-96-11) a 40-year-old Negress, in May, 1960, was found to suffer from mild diabetes and was given regular insulin, 10 units twice daily. About two weeks after therapy was commenced she developed a right-sided limp. At about this time a daughter noted her mother's inability to express her ideas. In June, she fell out of bed on two occasions. Thereafter there was complaint of pain and stiffness of the neck. She became more aphasic and unco-operative. A diagnosis of schizophrenia with catatonia accounted for her admission to Crownsville. She was

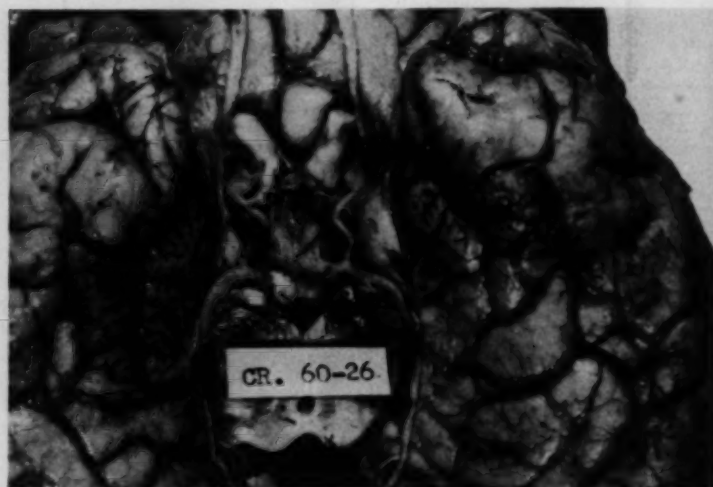


Fig. 18 (Walsh and Gass). M. M. (597-60) (Case 8). Herniation of the left gyrus rectus (right side of picture). Section showed oligodendrocytoma in the herniated cerebral tissue.

disoriented in regard to time but not place. Memory was considered as poor. On one occasion she was given 40 units of insulin inadvertently and she promptly developed a right hemiparesis which subsided after intravenous glucose was administered.

EXAMINATIONS showed the head turned to the left, eyes to the left. The pupils were small and reacted to light. There was bilateral papilledema. It was impossible to determine the visual acuity and to know if visual field defects were present. Dr. H. Reissman suspected brain tumor and arranged transfer to the University Hospital.

The patient was completely unco-operative and was found to have an extremely elevated blood sugar. This was rapidly brought to a normal level.

X-ray films showed a left frontal calcified area. A left carotid arteriogram indicated the presence of a mass in the left frontal lobe anteriorly. Following arteriography she developed a right hemiplegia. She was operated upon as an emergency.

At operation a small subdural hematoma was located over the tip of the left frontal lobe. There was tumor in the anterior portion of the lobe, hard and not cystic. Approximately five cm. of the anterior left frontal lobe was removed. The pathologist's report was protoplasmic astrocytoma, grade 3 (fig. 18).

Following the operation the patient did poorly. The blood sugar rose to 680 mg. percent and B.U.N. to 77 mg. percent shortly before death. This occurred three weeks after operation.

COMMENT. The two cases (7 and 8) do not establish herniation of the gyrus rectus as a clinical entity accounting for chiasmal

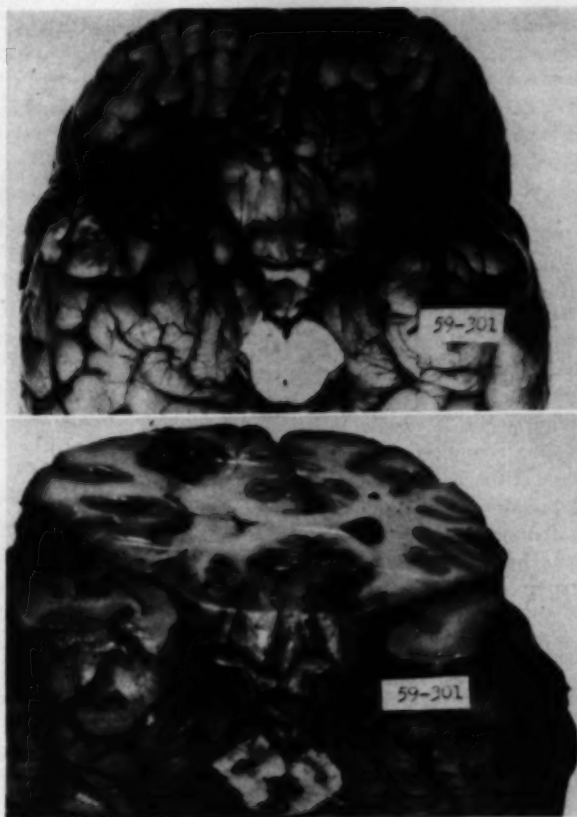
or optic nerve involvement but they suggest such is the case. In Case 7, the bitemporal field defects were not actually charted but undoubtedly were present. If they had been recognized prior to operation the fields would have had false localizing value. In Case 8 the gyrus, homolateral to the main body of the tumor, itself contained tumor.

We have observed several examples of herniation of the gyrus rectus, unilateral and bilateral, in children and in adults. It has been found when there was widespread swelling of the brain from whatever cause, following trauma, and with tumor anteriorly situated (Case 7). Necrosis of a prolapsed gyrus rectus was observed through the courtesy of Dr. Lindenberg. Also Dr. O. Solnitzky showed us such a specimen and another in which there was bilateral gyrus rectus herniation. Fischer* described such cases and produced a figure depicting bilateral herniation.

The possible ophthalmologic importance of gyrus rectus herniation (fig. 19) has not been adequately studied nor has it been reported upon to our knowledge. It well might

* Arch. f. klin. Chirurg., 200:213-226, 1940.

Fig. 19 (Walsh and Gass). Gyrus rectus herniation from trauma. A. J. (219-59) aged 58 years, a pedestrian, was struck by a car. There were fractures of the left tibia and fibula. The patient was stuporous and decerebrate 24 hours later. Burr holes were made. Bilateral subdural hematomas were found and evacuated. The patient never regained consciousness and died 48 hours after injury. There was hyperpyrexia before death. A fracture of the right parietal bone extended to the foramen magnum. (Above) Bilateral herniation of the gyrus rectus, more pronounced on the right. Cortical softening in areas of both anterior cerebral arteries, orbital branches. (Below) Note contusion hemorrhages. In the right frontal lobe the hemorrhage may have resulted from needling. There is extensive midline hemorrhage in the midbrain; this is secondary to pressure.



explain some cases of optic atrophy which follow injury at birth. If individuals exhibiting only optic atrophy, unilateral or bilateral, present at an early age were found at autopsy to have properly situated changes in the gyrus rectus and bone changes such as were found in Case 7, the significance of the entity would become more nearly established. Dr. David Clark has looked for sclerosis in the gyrus recti in some such cases and to this time has not found it; possibly the adequate circulation in this cerebral area explains the absence of residual damage.

CONCLUSION

Since deSchweinitz contributed to our knowledge of chiasmal and optic nerve involvements, many advances have been made

in diagnosis and therapy. Technical procedures now utilized routinely and improved therapy have made diagnosis more accurate and treatment safer. We regret being unable to add to the sum total of present knowledge in both regards. What has been presented here has possible value in emphasizing the intricacies of the symptomatology and pathology of chiasmal involvements and the necessity of co-ordinating our knowledge concerning them. Gyrus rectus herniation may ultimately be established as an important entity.

We are grateful for the continuing cooperation of our colleagues some of whom have been mentioned in the text.

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ASPIRATION OF CONGENITAL OR SOFT CATARACTS: A NEW TECHNIQUE*

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I. INTRODUCTION

A new technique for the aspiration of congenital cataracts, or soft cataracts of any etiology, in individuals under 30 years of age is presented. The lens is aspirated using a specially made No. 19 needle inserted through a scleral puncture, made by a knife needle, 1.5 mm. behind the limbus. This very small opening, which is only large enough to admit a No. 19 needle, practically eliminates wound complications and precludes vitreous loss. If the lens is not completely cataractous, a preliminary capsulotomy is done to permit softening of the lens by aqueous. When the lens has become completely opaque, which requires from two or three to several days, it can be aspirated quite easily leaving little or no lens material in the anterior chamber.

No general agreement exists as to the best method for removing congenital cataracts. Several different methods are available, each with its enthusiastic advocates. This situation is quickly substantiated by an even cursory review of the literature. The present paper was stimulated by presentations on the subject presented at the annual meeting of the American Ophthalmological Society in May, 1960. One of the essayists, Dr. Fredrick C. Cordes,¹ advocated linear extraction and the other, Dr. Ira S. Jones,² favored discission. Excellent arguments were advanced for each procedure.

The different techniques for the management of congenital cataract are: (1) iridectomy for optical reasons, (2) discission, (3) linear extraction, (4) aspiration, (5) Ziegler through-and-through discission, and (6) intracapsular extraction. Because of the

lack of unanimity of opinion regarding choice of operation, brief discussion of the various techniques seems justifiable as well as a brief review of the historical background and rationales for each procedure. At the same time I will attempt an evaluation of those procedures with which I have had experience. A complete review of the literature will not be attempted because of the numerous excellent reviews in recent years.³⁻⁷

II. REVIEW OF OPERATIVE PROCEDURES

1. IRIDECTOMY FOR OPTICAL REASONS

Iridectomy, for many, has been used to obtain improvement in vision for congenital cataracts, particularly the dense central type. The method is safe and often extremely helpful. However, the maximum vision of which the eye is capable usually is not obtained. The operation has been more widely used by European than American ophthalmologists. I have only occasionally resorted to this approach, although it does possess the virtue of simplicity and safety. It is of especial value in retarded children where fine vision is not essential.

2. DISCISSION

Discission, single or repeated as many times as needed, is probably the oldest of all operations for congenital cataract. Beard⁸ stated that needling was developed in ancient times as a result of experiences with the couching operation. Hard cataracts of older individuals were readily depressed by the couching needle whereas the soft cataract of childhood and youth was difficult to displace and, instead, the capsule usually tore. The lens would then undergo absorption. Wilder⁹ stated that although the ancients undoubtedly used the method, Percival Potts was given credit for the discovery in 1775. He ob-

* From the Department of Ophthalmology, Hospital of the University of Pennsylvania, Graduate School of the University of Pennsylvania, Philadelphia General Hospital, and the Children's Hospital of Philadelphia.

served that when the capsule of the lens was freely lacerated, the cataract subsequently was absorbed by the action of the aqueous. Conradi,¹⁰ 1797, introduced corneal puncture and opening of the anterior capsule. He also advised limiting the operation to soft or fluid cataracts. Cohn¹¹ in 1872, advised making the puncture at the limbus and Kuhnt,¹² in 1899, punctured subconjunctivally just behind the limbus. A further modification of discission was introduced by Moncreiff,¹³ in 1946. After making a wide opening in the anterior capsule, he used an anterior chamber irrigator to displace the lens material forward into the anterior chamber in front of the iris.

Hasket Derby¹⁴ in a classic treatise on congenital cataract, 1885, emphasized the importance of a widely dilated pupil. He stated that simple discission should never be done if the pupil failed to respond to a mydriatic. He felt that the degree of pupillary dilatation should be determined before deciding upon the type of surgery to be performed. If the pupil failed to dilate, he advised preliminary iridectomy three or four weeks before doing a discission. He stated that iridectomy diminished the amount of contact between cortical substance and iris and therefore minimized the danger of adhesions and secondary glaucoma. This rule is too often overlooked by present day ophthalmologists and, in my opinion is equally valid for all types of operations for congenital cataract. Failure to observe this rule can result in secondary pupillary block glaucoma or occlusion of the pupil by a dense membrane over the pupillary space. These are two of the commonest complications of surgery for congenital cataracts and may occur alone or associated with each other. They can be to a large extent prevented by good pupillary dilatation or by complete iridectomy if the pupil dilates poorly.

Discission was the technique that I was taught by Dr. Francis Heed Adler as a resident and the one that I employed during the first years of my practice. However, I now

rarely use it for several reasons. The method is simple but usually must be repeated several times. Each operation is accompanied by the hazards of general anesthesia as well as the dangers associated with the insertion of an instrument into the eye. The tendency to formation of posterior synechias by repeated operations and repeated exposure of a somewhat irritated iris to lens cortex must be recognized. Secondary glaucoma may result. There also is a tendency to organization of lens material and fibrin over the pupillary space to form a dense connective tissue membrane that may be extremely difficult to open. The danger of these complications and the length of time required for lens material to absorb necessitate a somewhat tedious period of postoperative care.

3. LINEAR EXTRACTION

The development of linear extraction naturally followed the introduction of cataract extraction through a corneal incision by Daviel in 1748. Gibson,¹⁵ 1811, used a much smaller incision for soft cataracts than for senile lenses with a large nucleus. The operation apparently was the same procedure which today is known as linear extraction. Gibson also performed a preliminary discission to soften the lens. He should therefore be regarded as the inventor of linear extraction for soft and membranous cataracts. Travers,¹⁶ 1814, used the same technique without a preliminary discission and made a quarter circle incision with a knife. Travers and Gibson both employed a lens spoon. Jaeger,¹⁷ in 1844, used the method and named it linear extraction. Graefe,¹⁸ 1865, after a trip through Europe, felt the method was falling into disfavor, even with Jaeger.

I found no further modifications of the technique of linear extraction in the literature until the work of Barkan,¹⁹ in 1932. Barkan recognized that discission was the most widely used method for operating soft cataracts in children and young adults. However, he stated his own preference for linear extraction, a technique with which he had be-

come familiar during three years as an assistant to Hess. He described certain of his own modifications to the technique. He emphasized the importance of an oblique keratome incision about two-mm. within the limbus. This type of incision, because of its valvelike nature, was self-sealing. Before inserting the keratome, he obtained wide pupillary dilatation by the subconjunctival injection of adrenalin at the limbus in the meridian of the corneal incision. This permitted more ready removal of the lens and retracted the pupillary border to a point peripheral to the inner lips of the wound. He also, after removal of the lens, filled the anterior chamber with saline. Later he²⁰ described making a preliminary stab wound through the cornea with a knife needle through which saline could be injected to refill the chamber.

Cordes,²¹ in an excellent article on the surgery of congenital cataracts, modified Barkan's technique by injecting air into the anterior chamber through a preplaced corneal puncture after removal of the lens. He, too, emphasized the necessity of a complete iridectomy whenever the pupil dilated poorly. He stated that the operation was contraindicated in the presence of membranous or thin cataract because of the danger of vitreous loss upon applying the capsule forceps. The technique described by Cordes is being widely used at present by many ophthalmic surgeons. Chandler²² performs linear extraction through a limbal incision which he closes with appositional sutures. He still more strongly emphasizes the need for complete iridectomy in the presence of poor pupillary dilatation.

Linear extraction as evolved by Barkan and Cordes is an excellent operation, but in my hands can be accompanied by very serious complications. Wound difficulties can occur. Capsular material may be caught in the incision at the time of operation or later, as may the iris or vitreous. Corneal edema may then occur as a late complication. Wound complications are sufficiently fre-

quent that I agree with Chandler that sutures should be used routinely if the method is employed. Vitreous loss during surgery is not unusual. Another difficulty is encountered with incomplete cataracts. Viscous lens material remains adherent to the posterior capsule and cannot be removed, a situation that is followed by slow absorption of the lens and its attendant complications. In this type of cataract a preliminary discission should be done prior to linear extraction. In my own experience the hazards of linear extraction tend to outweigh its advantages.

4. INTRACAPSULAR EXTRACTION

Intracapsular extraction has been looked upon with disfavor because of the great danger of vitreous loss caused by the force required to rupture the tough zonule in young individuals. Furthermore, a large incision is needed which leads to wound complications, especially in children where post-operative control is difficult. It is possible that the use of alpha chymotrypsin or a related enzyme may alter this outlook, but at present most ophthalmic surgeons warn against its use. Apparently the enzyme weakens the zonule sufficiently to permit cataract extraction but the ligamentum-hyaloidocapsulare remains attached so firmly that the face of the vitreous adheres to the lens with resultant vitreous loss.

5. ASPIRATION TECHNIQUE

Extraction of the lens by suction apparently dates back to antiquity. Hasket Derby stated that there was reason to believe that it was used as early as the fourth century. However, the first direct reference that he was able to cite was by Laugier,²³ in 1846. He made an opening in the sclera and introduced the point of the suction needle through the posterior capsule. Derby states that Laugier, at least, deserves credit for reviving interest in aspiration of cataract. Teale,²⁴ 1846, described an instrument he used for aspiration of the lens and surgical techniques that are employed today. Derby, however,

said that the method never found general favor and that it had not met with the appreciation which in his opinion it deserved. Teale used a suction tip connected to a rubber tube for oral suction. Derby used the same method but devised a shorter slightly smaller tip. Each employed an oblique corneal incision within the limbus. Hasket Derby reported results on 65 eyes. Bowman attached the tip to a syringe type of suction.

Other articles in the literature advocating aspiration of the lens were those by Dean,²⁵ 1926, Wilder,²⁶ 1928, and Blaess,²⁷ 1938. Dean also reported his own suction apparatus. Blaess was enthusiastic about the technique and especially recommended using the Hildreth lamp to visualize and aid in the removal of residual lens material. He reported his results on 37 eyes and mentioned the paucity of references in the literature to a method which he valued so highly. He also stated that the operation could be carried out in one, two, or three steps, depending upon the circumstances in each case. He employed a keratome incision four to five mm. long under a narrow corneal flap. I agree that aspiration of soft cataracts is an excellent operation and for several years have preferred it to others, using the method to be described later.

Daily²⁸ has used a similar method which he illustrated by a movie shown before the American Academy of Ophthalmology and Otolaryngology in 1958. He recently submitted a written description to me. He makes a small corneal incision and after opening the anterior capsule introduces a Fuchs' syringe which simultaneously irrigates and aspirates.

6. THROUGH-AND-THROUGH DISCISSION (ZIEGLER)

The Ziegler²⁹ technique of making a large V-shaped opening through the entire thickness of the lens never gained wide favor. Moncrieff stated that evaluation of the Ziegler method was difficult because few reports of its use could be found in the literature.

Authoritative opinions can be found in discussions of papers by Dean, 1926, and by Wilder, 1928. The Ziegler procedure was disapproved by Dean, Greenwood, Lancaster, and Wilder largely on the grounds that they were opposed to trauma of the vitreous. Benedict and Weiner,³⁰ on the other hand, endorsed the Ziegler operation and stated that they had used it extensively. Benedict³¹ has told me recently that he preferred this operation to any other for congenital cataract and had used it until his recent retirement from ophthalmic surgery.

My own experience with the Ziegler operation has been limited to a small number of eyes. In these I have encountered no complications. In general I have employed it for thin or membranous lenses and find it very valuable for this purpose. Only one operation is required and it is very easy to do. I have not used it more because of its general lack of approval, although I would be somewhat concerned about the danger of secondary glaucoma in eyes with lenses of normal size. The treatment of this type of glaucoma consists of washing out lens material which, because of the incision through the posterior capsule, would be very likely accompanied by vitreous loss. On the other hand, those who have used the method extensively state that glaucoma does not develop. Many ophthalmic surgeons also object to the method because they feel that incision into the vitreous predisposes to retinal detachment. As pointed out by Benedict, the majority of operations for congenital cataract require a posterior capsulotomy as a final step before good vision can be obtained. He raised the question as to why it should matter whether the face of the vitreous were incised at the first operation or as the final step.

It is obvious that the ophthalmic surgeon has a variety of procedures from which to choose for operating congenital cataract. Considerable, often enthusiastic, support for each technique can be obtained from the literature. Part of the explanation for the



Fig. 1 (Scheie). Thin-walled No.-19 needle inserted into anterior chamber, bevel down.

great difference of opinion in the management of congenital cataract probably results from the fact that only a few ophthalmic surgeons see a sufficiently large number of congenital cataracts to give various methods a thorough trial, and as a result a broad cross section of opinion is unobtainable. The young ophthalmologist, therefore, usually employs the technique of his chief or preceptor and has little opportunity to broaden his experience.

Since finishing my residency, I have had fairly extensive experience with discission, linear extraction, and finally aspiration. In my hands, this method is safer and more satisfactory than any other. It can be employed for congenital cataracts or soft cataracts, including those due to trauma in young persons up to 30 years of age. A preliminary discission should be done if the cataract is incomplete to permit digestion and softening of lens material which can then be aspirated leaving little or no residual lens material. If poor pupillary dilatation is obtained, complete iridectomy is done in combination with aspiration or with the preliminary needling.

III. MY TECHNIQUE FOR ASPIRATION

The aspiration is done under general anesthesia in infants and children. In older individuals who can co-operate it is done

under local anesthesia. Maximum pupillary dilatation is obtained preoperatively by the instillation of atropine sulfate (one percent) and phenylephrine HCl (10 percent).

The procedure varies somewhat depending upon whether or not the cataract is complete and whether or not good pupillary dilatation can be obtained preoperatively by mydriatics.

A. COMPLETE CATARACT

When the cataract is complete, a small conjunctival flap is reflected toward the limbus. An eye speculum is inserted and a superior rectus suture is placed. A small conjunctival flap is dissected toward the limbus superiorly. The eye is fixed with a fixation forceps at the 6-o'clock position and a Ziegler type knife needle is inserted in a plane parallel to the iris 1.5 to 2.0 mm. behind the limbus. A wide cruciate incision is made through the lens capsule and the knife needle withdrawn, enlarging the scleral opening very slightly as it is removed to create a puncture just large enough to admit the needle and for suction.

The needle is a specially made thin-wall No.-19 needle with an oval tip of the type described by Atkinson²² for retrobulbar anesthesia. It is inserted, bevel down, through the knife-needle incision at the 12-o'clock position (fig. 1). Because the needle is made

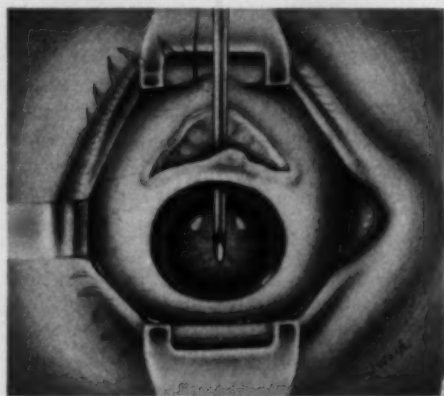


Fig. 2 (Scheie). Needle rotated, turning aperture forward prior to aspirating lens material.

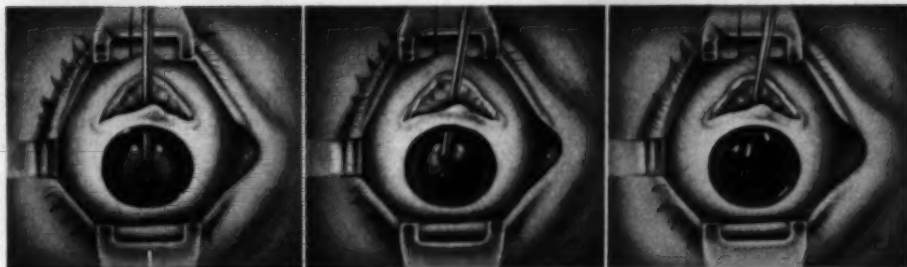


Fig. 3 (Scheie). Needle withdrawn as lens material is aspirated.

with a thin wall, the aperture is equivalent to that of a No.-18 needle. It is attached to a two-cc. syringe containing approximately 0.25 cc. of saline solution.

When the tip of the needle is at the lower pupillary border, the needle is rotated so that the bevel is turned forward with the aperture facing the cornea (fig. 2). This prevents injury to the vitreous when suction is applied. This point in technique was first made by Dean. I have never seen damage to the corneal endothelium occur from the force of the suction or needle tip.

With the needle in place, suction is created by withdrawing the plunger of the syringe. If the lens does not aspirate readily, fluid can be forced into the anterior chamber and sucked out several times which helps to break up and remove the lens material. When the

cataract is complete, however, there is usually no difficulty in removing the lens material. As the lens material is aspirated, the tip of the needle can be directed to various positions in the anterior chamber to gather up any material that remains. It is of interest that even dense central nuclear plaques or membrane can be sucked into the lumen of the needle and removed. When the chamber is clear, the needle is removed (fig. 3). If lens material remains, the needle can be inserted into the chamber more than once by injecting saline to deepen the chamber as the needle is inserted. This protects the face of the vitreous.

Occasionally the pupillary border is displaced as the needle is withdrawn, indicating that the iris is caught in the scleral puncture. It can be freed by directing a current of

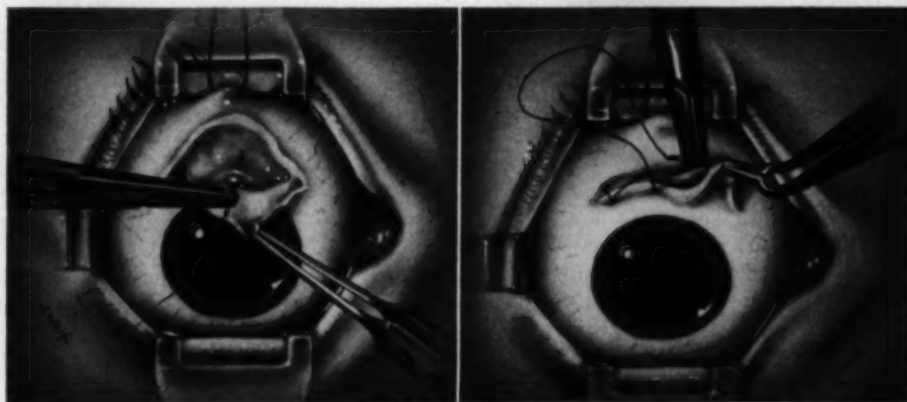


Fig. 5 (Scheie). (Left) Scleral puncture tightly closed by 6/0 mild chromic catgut.
(Right) Conjunctiva incision closed with running suture.



Fig. 5 (Scheie). Ripening operation performed by making a cruciate incision in lens capsule with knife-needle.

saline into the opening by an anterior chamber irrigator held against the incision. To insure prompt reformation of the chamber, even though the incision is small, a 6-0 mild chromic catgut appositional suture with an atraumatic needle is placed across the knife-needle incision (fig. 4). Finally, the conjunctiva is closed. Pupillary dilatation is maintained postoperatively with the continued use of atropine and if necessary phenylephrine (10 percent).

B. INCOMPLETE CATARACT

If the cataract is incomplete, a preliminary needling should be done. A knife-needle is inserted into the anterior chamber through the conjunctiva and sclera about 1.5 to 2.0 mm. back of the limbus (fig. 5). A large cruciate incision is made in the anterior lens capsule. No attempt is made to stir up the cortex because of danger of injury to the posterior capsule. The eye is observed carefully for the next few days and when the lens is completely opaque and softened, as a result of action of the aqueous, aspiration is done. The interval is usually two or three days to a week. At that time, the operation as described for complete cataract is carried out. A conjunctival flap is turned, but another knife-needle incision usually is not

necessary because the No.-19 needle can be inserted through the original puncture made for the discission (fig. 6). Aspiration of the lens material is done as previously described and the wound closure is identical. Pupillary dilatation, again, must be maintained postoperatively.

C. ASPIRATION WITH INCOMPLETE PUPILARY DILATATION

If the pupil does not dilate well preoperatively, the above operations must be combined with complete iridectomy. The technique is modified somewhat. A conjunctival flap is reflected toward the limbus. The knife-needle incision is made as already described and, except that following the discission, the wound is enlarged slightly but to no more than three mm. Slight pressure on the globe with the lips of the knife-needle incision separated permits the root of the iris to present into the opening. The iris is teased out by hand-over-hand action with iris forceps and a complete iridectomy done. Care is taken to replace the iris pillars. If the cataract is complete the No.-19 needle is then inserted as described and the lens removed. If the cataract is incomplete, the conjunctival incision is closed and removal of the lens material is done several days later as already described under Section B.



Fig. 6 (Scheie). Previously made puncture with Ziegler knife visible after turning conjunctival flap.

IV. DISCUSSION

I have used this simple technique for aspiration during the past eight years almost to the exclusion of other methods because of its simplicity and safety. The very small incision permits almost no wound complications and vitreous loss is not a factor. I have used the method to aspirate lens material in one eye with secondary glaucoma following through-and-through dissection for subluxated lenses. The lens material was easily aspirated and no vitreous was able to escape. Adhesions of the iris or capsular material to the wound are less likely to occur than with larger incisions. If they do, the adhesions are very small and posterior to the corneal endothelium, thereby avoiding late corneal edema.

The necessity of performing a complete iridectomy in the presence of poor pupillary dilatation has been pointed out by Hasket Derby, Cordes, Chandler, and others. It is re-emphasized here. In my experience the commonest cause of poor vision following

congenital cataract is failure to observe this rule. Other complications, such as secondary glaucoma due to lens material, vitreous loss, infection, late retinal detachment, and all of the other hazards of operating congenital cataracts need not be discussed as they have been reviewed elsewhere.

This aspiration technique is valuable for the removal of cataracts due to any etiology occurring in individuals up to 30 years of age before the nucleus is firmly formed. It is my operation of choice for juvenile cataracts and is very helpful in the management of traumatic cataracts in young people.

V. SUMMARY

The historical background of various procedures for congenital cataract is briefly reviewed. An attempt has been made to evaluate each method with which I have had personal experience. A modified technique for aspiration of congenital cataracts or soft cataracts due to any etiology is presented.

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HEMIANOPIA AND ASSOCIATED SYMPTOMS DUE TO PARIETOTEMPORAL LOBE LESIONS*

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This evening I would like to focus my remarks on hemianopia resulting from lesions in the parietotemporal regions. Such lesions commonly induce homonymous scotomas in the contralateral visual fields and these are designated hemianopias, even when less than half the visual fields are involved, or quadranopias, even when less than the quadrants are involved. These field defects are amenable to quantification in a way exceeding perhaps any other neurologic sign and may be particularly valuable in following the course of the disease. Valuable, but less precise, is the information which the fields give us as to topical localization. For this we must take advantage of other information which the history and examination of the patient gives us and relate these to the hemianopia. It will be the purpose of this talk, therefore, to emphasize the associated symptomatology that accompanies the various types of hemianopia.

By way of introduction I might review some of the anatomic bases for the field defects which we will be considering. Then we

will briefly consider hemianopia per se but I would like to spend most of my allotted time on case presentations illustrating the associated signs and symptoms that characteristically accompany lesions in the parieto-occipital regions.

ANATOMIC CONSIDERATIONS

The parieto-temporal area comprises the middle portion of the cerebrum. The parietal lobe is bounded anteriorly by the central fissure of Rolando, posteriorly by an arbitrary line separating it from the occipital lobe, and inferiorly by the lateral fissure of Sylvius. On its medial surface the parietal lobe is bounded posteriorly by the parieto-occipital fissure. The temporal lobe is bounded superiorly by the fissure of Sylvius and posteriorly by an arbitrary line separating it from the occipital lobe. On the inferior surface of the brain the temporal lobe extends medially to abut against the optic tracts and cerebral peduncles.

Noteworthy landmarks on the lateral surface of the parietotemporal area are: the angular gyrus which, in the dominant hemisphere, contains the centers for recognition of written words and symbols; the supramarginal gyrus, at the termination of the Sylvian

* From the Howe Laboratory of Ophthalmology, Harvard University Medical School, and the Massachusetts Eye and Ear Infirmary. The Snell Memorial Lecture presented at Rochester, New York, April 15, 1960.

fissure, which almost certainly co-ordinates some of the higher visual functions; the gyrus at the junction of the Rolandic and Sylvian fissures which, in the dominant hemisphere, is concerned with recognition of the spoken word; and the postcentral gyrus just behind the Rolandic fissure which represents the somesthetic sense of the contralateral half of the body. A noteworthy and pertinent landmark on the inferior surface of the brain is the hippocampal gyrus, the most medial of the longitudinal gyri of the temporal lobe, and the hooklike anterior extension of the hippocampal gyrus called the uncus.

From the ophthalmologic point of view, the most significant content of the parietotemporal area is the visual radiation. This enters the cerebral hemisphere from the lateral geniculate body, to form the posterior end of the internal capsule. Its fibers fan out about the lateral ventricles in such a manner that those destined for the upper occipital area pass directly backward through the inferior portion of the parietal lobe while those destined for the lower occipital area pass forward into the temporal horn (Meyer's loop) before being directed backward in the substance of the temporal lobe. The upper and lower fibers of the visual radiation represent the upper and lower portions of the retinal periphery respectively while the mass of intermediate fibers represent the macular areas.

CHARACTER OF HEMIANOPIA

Homonymous hemianopia indicates, of course, a lesion in the opposite half of the brain. Those hemianopias due to lesions

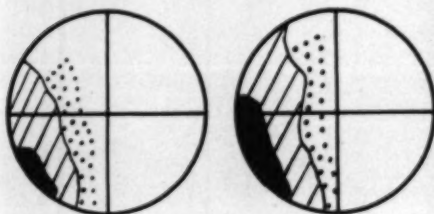


Fig. 1 (Cogan). Field defect characteristic of a parietal lobe lesion. The patient had a metastatic carcinoma of the right parietal lobe.

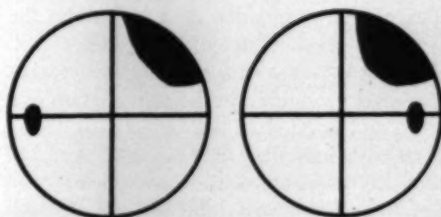


Fig. 2 (Cogan). Field defect characteristic of a temporal lobe lesion. The patient was a 40-year-old man who presented with the complaint of intermittent foul odors (uncinate pits). At surgery he was found to have a glioma of the temporal lobe.

within the cerebrum have certain topologic features: parietal lobe lesions induce field defects initially in the lower quadrants (fig. 1), whereas temporal lobe lesions induce defects initially in the upper quadrants (figs. 2 and 3). Both spare the central area of fixation ("macular sparing") at first. The scotomas in the two eyes are usually symmetric but occasionally with temporal lobe lesions and more rarely with parietal lobe lesions, the scotoma in one eye may be more extensive than that in the other eye.

Lesions in the anterior portion of the occipital lobe may produce field defects that simulate those due to parietotemporal lesions but lesions in the posterior portion of the occipital lobe differ in producing sectorlike field defects extending from the point of fixation. These latter are highly characteristic of lesions in the occipital pole and easily distinguishable from parietotemporal lesions.

The border of a field defect gives some

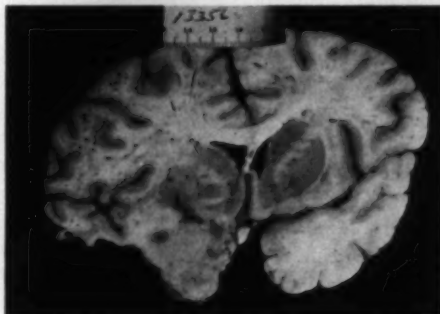


Fig. 3 (Cogan). Brain specimen of foregoing case. A considerable portion of the temporal lobe had been excised at surgery but residual tumor can be seen replacing the rest of the temporal lobe.

idea of the progression of a lesion and the potential reversibility of the field defect. Those scotomas with a shelving border, that is wherein a significant difference exists for small and large sized test objects, are interpreted as indicating a functional and potentially reversible disturbance, whereas the steep borders wherein the edge of the scotoma is the same for small and large sized test objects are interpreted as indicating destructive and irreversible lesions.

Hemianopias from parietotemporal lesions are not always easy to distinguish from tract lesions. However, when any of the following signs are present, the lesion almost always involves the tract. Decrease of visual acuity may result from associated involvement of the chiasm with tract lesions but never results from simple parietotemporal disease since the acuity measured in half a macula is as good as in a whole macula. Optic atrophy is presumptive evidence of tract involvement since cerebral lesions do not ordinarily cause transneuronal degeneration. Wernicke's hemianopic pupillary reaction should on theoretical grounds be of great help but practically it is of little value for lack of a satisfactory instrument for its testing. Perhaps most useful in differentiating tract and cerebral lesions is the presence of associated cerebrogenic symptoms which will be discussed subsequently.

SYMPTOMS RESULTING FROM HEMIANOPIA PER SE

The rate of onset of a hemianopia determines to a large extent the severity of the symptoms which it causes. With an insidious onset the patient may not be aware of its presence and wonder why he or she bumps into objects on one side. The chief complaint may be in reading and such patients often present themselves as refractive problems. On questioning, however, the patient with a right hemianopia states that he sees only parts of a word and has to read slowly, whereas the patient with a left hemianopia reads across a page with facility but gets

mixed up in returning to the next line. (I am told it is the reverse in Arabic where the reading is from right to left.)

Hemianopias which come on precipitously are generally recognized as such by the patient although this is not invariably so and one type, generally occurring in a confused patient, is characterized by persistent denial of the hemianopia (Anton's syndrome).

Rarely patients with hemianopia complain of "after-images" in their blind field. This has been likened to perservation in neurologic semeiology but actually it appears to be more of a filling-in similar to that which normally occurs in the region of the blind spot. When an object disappears into the blind field it is interpreted as being there even though it may have been moved away. The patient thus having information that an object has been moved into the blind field and not that it has been moved away, calls this an after-image, which in a sense it is.

ASSOCIATED SIGNS AND SYMPTOMS

In recent years an attempt has been made to separate symptoms involving visual functions into those arising from the parietotemporal region of the dominant and those from the nondominant hemispheres. In keeping with such a division, the subsequent discussion will revolve around: (1) symptoms common to lesions in either hemisphere; (2) symptoms found predominantly with lesions in the dominant hemisphere; (3) symptoms found predominantly with lesions in the nondominant hemisphere; and (4) symptoms with lesions that involve simultaneously both hemispheres. Hemianopia is one of the presenting symptoms in practically all the cases.

1. SIGNS AND SYMPTOMS COMMON TO BOTH HEMISPHERES

The optokinetic response is often abnormal with lesions in the parietal area of either hemisphere. The movement of the eyes in following the stripes of a rotating drum, for instance, are diminished when

the objects are directed toward the side of the lesion as compared with movement to the normal side. Nystagmus may be absent to one side or may be asymmetrically more fatiguable. This unilateral abnormality of the optokinetic response is particularly characteristic of parietal lobe lesions and as such is frequently associated with hemianopia but it does not depend on the hemianopia. Thus it is normal with hemianopias of tract origin and conversely it may be abnormal with dorsal parietal lesions in which the visual radiations are not involved. It may also be abnormal with brainstem lesions in which the visual functions are normal. Thus the optokinetic abnormality with parietal lobe lesions appears to depend on involvement of the conjugate motor pathways rather than the sensory pathways although the two must be closely associated.

The following are two illustrations of a pathologic optokinetic response due to a parietal lesion without involvement of the visual pathways.

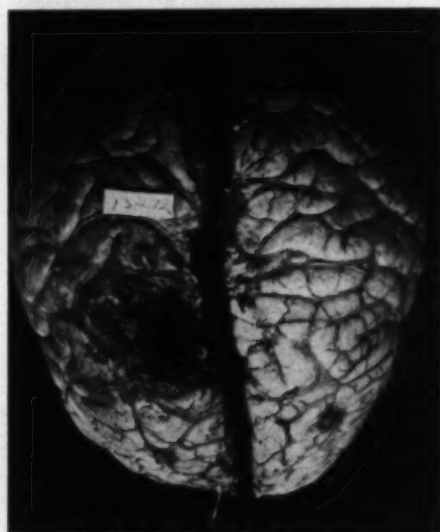


Fig. 4 (Cogan). Lesion (meningioma) of the dorsal parietal region in a patient who had full visual fields but unilateral absence of the optokinetic response.



Fig. 5 (Cogan). Deviation of the eyes on attempted closure of the lids (spasticity of conjugate gaze) with a gliomatous cyst in the left parietal region. The eyes deviate to the side opposite the lesion.

Case 1. A 48-year-old woman with a parasagittal meningioma involving the dorsal parietal area of the brain (fig. 4). The presenting symptoms were headache and paralysis of the left foot. Despite alert and reliable cooperation on the part of the patient no field defect was present but the optokinetic response was completely absent on rotation of objects toward the patient's right.

The patient was operated upon but died the following day.

Case 2. A young man who had an extensive right frontoparietal glioblastoma multiforme, involving particularly the dorsal parietal region. Again the optokinetic response was not elicitable on rotation of objects to the patient's right although the visual fields were normal.

The significance of these two cases rests not only in showing that the optokinetic abnormality is independent of the visual function but also in suggesting that the optomotor fibers responsible for the optokinetic reflex course dorsal to the visual radiation in the parietal lobe.

Conjugate deviation of the eyes with forced closure of the lids, the so-called spasm of conjugate gaze, is also a cognate sign of parietal lobe disease and will occur with lesions in either hemisphere (fig. 5). The patient is asked to close his eyes while the examiner forcibly opens them. Instead of the usual upward or upward and divergent movement (Bell's phenomenon), the eyes of patients with unilateral parietal lobe lesions frequently show a conjugate deviation of the eyes to the side opposite the lesion. This spasticity of conjugate gaze is an important correlative sign of unilateral parietal disease, occurring with lesions in either hemisphere but its value is somewhat limited by the fact that it also occurs with brainstem lesions

and occasionally in otherwise normal persons.

Somesthetic disturbances also occur characteristically with parietal lobe lesions, especially deep-seated ones, but insofar as they do not involve visual functions they will be merely listed: loss of two point discrimination, failure to recognize coins and other objects placed in the hand (astereognosia), loss of vibration sense and a feeling of numbness on the opposite side of the body.

Temporal lobe lesions do not ordinarily cause the asymmetry in the opticokinetic response nor the spasticity of conjugate gaze with forced closure of the lids unless the parietal lobe is also involved. Temporal lobe lesions, however, often induce profound defects in memory due to involvement of the hippocampus and cause brainstem signs of neuro-ophthalmic interest (nyctagmus, paralysis of upward gaze, anisocoria, and occasionally third-nerve paralysis). Optic atrophy may result from extension of the lesion to the geniculate body and optic tract.

Flashes of light, pin wheel photopsia (lateralized in the opposite field), and formed hallucinations may occur with irritative lesions in the parietotemporal lobe similar to, and often in association with, convulsive seizures. These are especially frequent with post traumatic scars and calcified lesions of whatever origin.

Finally, patients with temporal lobe lesions are constantly threatened by herniation of the brain through the tentorium. This event, usually heralded by dilatation of the homolateral pupil and occasionally other third nerve signs, is an ominous sign since the resultant compression of the brainstem can cause sudden death of the patient.

2. SYMPTOMS ASSOCIATED WITH LESIONS OF THE DOMINANT HEMISPHERE

The fact that man has a unilateral word symbol center causes one hemisphere to be dominant. This center is situated in the parietotemporal area and lesions of it induce a group of symptoms that involve faulty

comprehension of the spoken or written word. Failure to understand written symbols is alexia. There are endless types of aphasia many of which involve the visual functions and are collectively called the visual agnosias.

The more common aphasias and other symptoms associated with parietotemporal lobe disease of the dominant hemisphere are collectively referred to as Gerstman's syndrome and consist of: agraphia (inability to write), acalculia (inability to do simple arithmetic problems), body agnosia (inability to identify the parts of one's own or other's body), and confusion of right and left handedness. These symptoms together with alexia are seen most commonly with lesions of the dominant (usually left) hemisphere although some of them may occur as isolated symptoms with lesions in the nondominant hemisphere.

Typical examples of Gerstman's syndrome with homonymous hemianopia follow:

Case 3. A 41-year-old man with right-sided homonymous hemianopia due to left parieto-occipital glioblastoma multiforme. Aside from the scotoma and an inability to understand the written word (alexia), the patient was unable to make simple calculations (serial subtraction of seven from 100); he repeatedly confused his right and left sides; and he was unable to identify parts of his body or to distinguish between his fingers and those of the examiners when they were intertwined. Also of interest was a disturbance of visual depth sense as evidenced by the fact that the visual test chart placed at 20 feet was thought to be within touchable distance.

Case 4. A 47-year-old woman who developed a subdural empyema following evacuation of a hematoma over the left parietal area. The presenting symptom was right-sided convulsions but on examination she was found to have a right hemianopia, a repeated misidentification of her right fingers as those of the examiner, a pathologically faulty distinction of right and left sides, an inability to write (agraphia) or to make simple calculations (acalculia) and a partial motor aphasia.

Case 5. A 70-year-old woman whose relevant symptoms began with an inability to talk, a smacking of lips, and a transient stupor in which inability to name objects (motor aphasia) was an early and prominent symptom. This was shortly followed by convulsions which were preceded by the lip smacking. Examination revealed a right homonymous hemianopia, a loss of feeling and of strength in

the right hand and a prominent feeling that the right hand and arm did not belong to her.

Since the patient had severe hypertension, a cerebrovascular accident was the initial diagnosis. However, the patient continued to have convulsive episodes following the same pattern and gradually developed loss of all sensation on her right side. Craniotomy revealed a seminecrotic glioblastoma in the left temporo-parieto-occipital area.

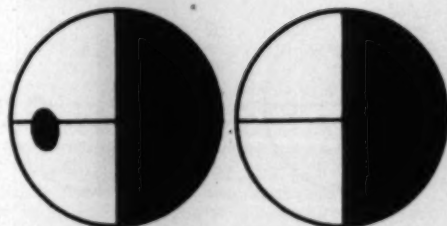
The most pertinent aphasia from the ophthalmologic point of view is that in which the patient is unable to interpret the written word (verbal alexia) or letter (literal alexia). This is associated most particularly with lesions in the angular gyrus of the dominant hemisphere (figs. 6 and 7). In its purest form the patient retains normal comprehension of the spoken word and may be able to write normally on dictation but then be unable to read what he has written! In its most marked form the patient loses comprehension not only of words and letters but of pictures as well. Curiously, the initial loss of word identification is not necessarily that for complex words. Often the identifiability is lost for simple words while being retained for complex words.

To be significant the symptom of alexia must stand out conspicuously. It should not be confused with a general intellectual impairment and adequate visual acuity should be proved by a copying test.

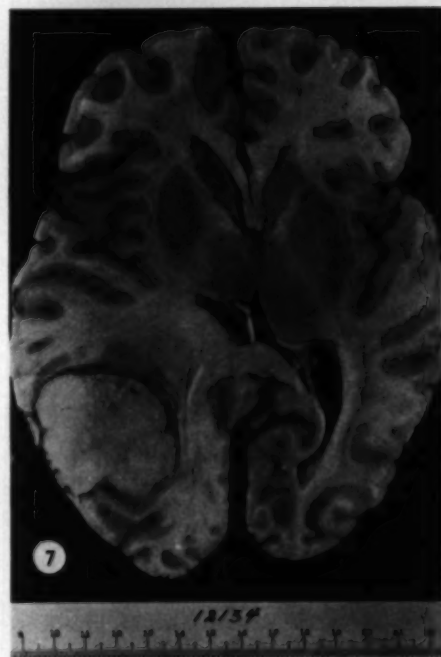
The following are some illustrative cases in which alexia was one of the presenting symptoms of a parietotemporal lesion in the dominant hemisphere.

Case 6. A 52-year-old physician with presumed metastatic lesion in the left parietal region. Alexia was one of the presenting symptoms and was characterized by an inability to recognize simple words such as "seal" and "all" but proper recognition of some complex words such as "ammonium hydroxide." Gradually the patient lost comprehension for all words and most alphabetical letters (literal alexia) but he did retain adequate recognition of numbers. Even at the stage of profound alexia he carried on a stream of talk which appeared quite normal.

Case 7. A 57-year-old man was admitted to the hospital with fatigue, amnesia, and personality changes. More specifically he complained of difficulty reading. He could not recognize printed words or letters and, although he could write well, he could not read what he had written. He could not



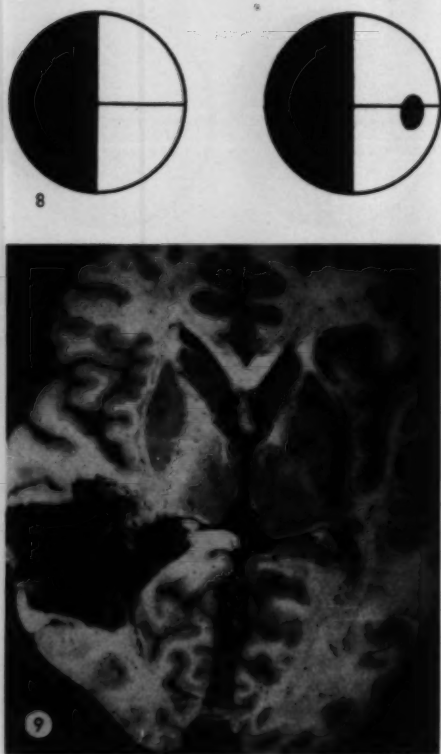
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identify the large letter E on the Snellen chart although he could be shown, by copying, to have an acuity of 20/20. Homonymous hemianopia was present on the right side but the optokinetic response was symmetric to the two sides.

The patient was found to have Hodgkin's disease and the cerebral lesions were those of multifocal leukoencephalopathy. (The present case is included in those described by Anstrom and Richardson: *Brain*, 81:93, 1958.)

Case 8. A 24-year old man had a head injury at



Figs. 8 and 9 (Cogan). Left-sided homonymous hemianopia and brain lesion (hematoma) on the nondominant side. The patient (Case 19) presented with spatial disorientation.

the age of three years and had never been able to read. Examination showed an absent opticokinetic response on rotating the drum to the patient's left and a profound alexia in which the patient was unable to make out such simple words as "the" and "on." He could identify only five letters of the alphabet (B, O, A, R, and S) and yet he was an able machinist and replied to verbal stimuli with intelligence. The visual fields were full and neurologic examination revealed nothing of significance other than a dominant left handedness.

The following several cases are instances in which less common aspects of the Gerstman syndrome or ancillary features were associated with lesions of the left parietotemporal region.

Case 9. A 48-year-old man, a hairdresser, whose initial complaint was recurrent inability to make change for his customers (acalculia). Each episode

lasted several minutes only but was so profound at the time that he was unable to do the simplest calculations. In the course of the next few months he complained of increasing headaches, dizziness, and forgetfulness, and finally inability to talk or read. Visual fields were not done until later. Ventriculography followed by craniotomy revealed a glioblastoma in the left occipitoparietal area. The occipital lobe and much of the parietal lobe were excised.

One year later the headaches recurred and this time with attacks of blindness. Fields showed a right-sided hemianopia and a quadrantic defect in the lower quadrant of the opposite side.

Case 10. A 26-year-old man with a parietotemporal lobe lesion due presumably to multiple sclerosis. The symptoms began with a numbness and weakness of the right arm, diplopia, slurring of speech, and inability to express himself, difficulty to write or to read. None of these symptoms were profound. Examination revealed a partial right homonymous hemianopia, a defective opticokinetic response on rotation of the field to the patient's left, and a limitation of adduction on gaze to either side with concomitant nystagmus of the abducting eye.

3. SYMPTOMS ASSOCIATED WITH LESIONS OF THE NONDOMINANT HEMISPHERE

The function which appears to be a prerogative of the nondominant parietotemporal region is that of visuospatial recognition. Lesions in this region cause, in addition to the hemianopia on the nondominant side, a loss of orientation in previously familiar surroundings (topographic agnosia) and an inability to construct simple architectural plans or geometric designs (constructional apraxia). Associated symptoms are an inability to put on one's clothes (dressing apraxia) and a curious disorientation of objects held in the hand. A striking illustration of the latter is the patient, described subsequently, who persistently held objects upside down. The proneness to auto accidents seems also to be significantly associated with lesions in the nondominant parietotemporal region (figs. 8 and 9).

These signs and symptoms appear to be about as common with lesions in the temporal as in the parietal lobe and the hemianopic scotoma may accordingly be denser in either the upper or lower quadrants. But in evaluating these symptoms it is important to make sure that the intellect in other spheres of activity (calculation, orientation as to time

and historic events) is relatively intact. One should make a diagnosis of topographic agnosia, constructional apraxia, or dressing apraxia only when these symptoms stand out conspicuously and are not merely part of a general intellectual deterioration.

Topographic agnosia is manifest by patients becoming lost in formerly familiar surroundings. Frequent histories are those of loss of way while driving one's car, driving on the wrong side of the street (with frequent auto accidents), or inability to find one's way to the bathroom in one's own home. While the patients may know just where they want to go and can visualize their ultimate destination they lose their sense of "here-to-thereness" and become absurdly dependent on others to tell them which way to turn.

Illustrative cases of topographic agnosia follow:

Case 11. A 60-year-old physician suddenly developed a vague visual complaint which in retrospect he believed to be attributable to a left hemianopia. Setting out for his ophthalmologist's office, he had no difficulty finding his garage and car but instead of getting into the front seat of his car he entered the left rear door. Correcting this error he had so much difficulty with the steering wheel and ignition that the attendant noted the unusual behavior. However, the patient drove the car out of the garage adequately and headed in the proper direction. On the way he became confused, although this region had been thoroughly familiar territory. In consequence of the confusion, he parked the car and summoned a taxi. He had no difficulty in giving directions where he wanted to go. Yet he noted that none of the streets seemed familiar to him. He did recognize the building, however, once that he arrived there and had no difficulty in settling with the cab driver or in giving his doctor an objective description of his visual space difficulties.

As he said, he could visualize where he was and where he wanted to go but had no idea of how to get from one place to the other. He was lost even in such familiar surroundings as between his office and a club where he had customarily lunched for years. Nor could he describe the streets abutting the local park although he had always lived in its vicinity. Yet he had normal facility in other spheres of activity as evidenced by his effective execution of income tax forms, facility in reading, and comprehension of musical scores.

Initially the patient had a left homonymous hemianopia but in the subsequent months this receded to a left upper quadrupia. The optokinetic

response was symmetric at all times. Neurologically he showed a diminution of vibration sense and mild hyper-reflexia on the left. The presumptive diagnosis was a cerebrovascular accident affecting particularly the right temporal area.

Case 12. A 64-year-old physician whose relevant symptoms began one year previously when he lost his way while driving his car; had difficulty in finding the bathroom in his own house; and got mixed up while sailing in familiar waters. Although these symptoms were evident and annoying to him, he was able to continue surgery for some time. When finally he gave up surgery he remarked, "I could still do an appendectomy if I could find my way to the hospital." About this time he was observed to put shoes on the wrong feet and to have difficulty in getting into the proper legs of his pants. Yet he could read well and had good insight into his symptoms.

On testing he was found unable to sketch the position of the organs in the abdomen, to draw a floor plan of his house or of the bridges over the Cape Cod canal with which he had been familiar since boyhood. In making a clock-face or daisy he misplaced the numbers or petals on the left side and in bisecting a line he made the right half one fourth that of the left. Eventually he was unable to copy the simplest block design or to assemble a simple profile. While in the hospital, he was observed to get mixed up abnormally as to where his room was in relation to the nurses station and to other rooms. Visual fields showed a left homonymous hemianopia with sparing of macula. Psychomotor testing was interpreted as showing a "high-over" level of verbal intelligence.

Craniotomy revealed an infiltrative tumor two cm. deep in the parieto-occipital area. The patient died a few months later.

Case 13. A 50-year-old housewife who developed intermittent headaches in the right parietal region, drove her car "all over the road," and lost her way in what had been familiar territory. She was unable to find a neighbor's house in an environment where she had lived for 25 years. She had also volunteered that the furniture in her living room looked unfamiliar to her. More recently she complained of her neck being painful and stiff.

On the first examination about six weeks after the onset, a left homonymous hemianopia was present. This was most dense in the upper quadrants. The discs were abnormally blurred but not elevated. Neurologically the patient was found to have a left facial weakness, nuchal rigidity, slight sensory impairment of the left, a cerebrospinal fluid pressure of 290 and a total protein of 84 mg. percent. A right arteriogram disclosed a mass in the right temporal lobe.

The right temporal lobe was partially resected (leaving the anterior tip) together with the inferior half of the left occipital lobe. A temporal lobe herniation was visualized and relieved. The angular and supramarginal gyri were left intact. Microscopy revealed a glioblastoma multiforme.

Postoperatively, a dense hemianopia persisted

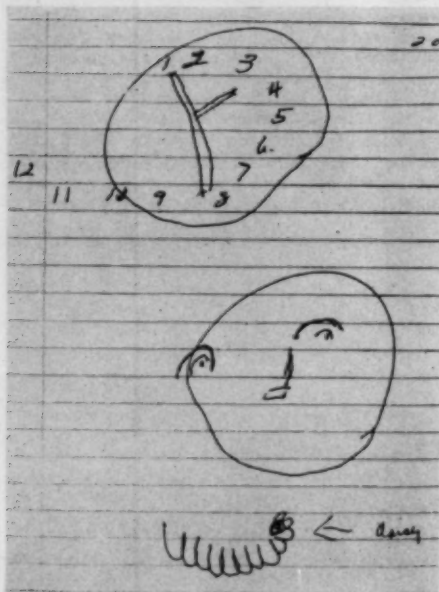


Fig. 10 (Cogan). Constructional apraxia in a patient (Case 14) with a lesion of the nondominant hemisphere. Noteworthy is the disarray and neglect of figures on the left-hand side of the drawing.

and the patient complained that the lines of reading matter seemed to run together. She had no difficulty in threading a needle, however. The opticokinetic response was symmetric to the two sides but the eyes consistently deviated to the left with forced closure of the lids. Psychometric studies indicated that the patient had particular difficulty in assembling puzzle pieces.

Over the ensuing 18 months the patient's course was characterized by severe depression, progressive left hemiplegia, left hemi-anesthesia, stupor, and death. Autopsy revealed residual glioblastoma multiforme.

Constructional apraxia is an inability to make diagrams from memory or to copy geometric designs. One patient expressed it as an inability to "encompass a panorama." Like topographic agnosia with which it is often associated, constructional apraxia represents a disturbance of visuospatial organization. It is often manifest by neglect of the left side of diagrams, accompanied by a striking lack of insight, although other spheres of intellectual activity are well preserved.

Common tests for constructional apraxia are those involved in drawing a floor plan of one's house, drawing the face of a clock to indicate a specified time, or the petals of a daisy. Also effective tests are copying triangles, squares, and cubes either by a drawing or by arranging match sticks.

Some examples of constructional apraxia follow:

Case 14. A 68-year-old man whose initial complaint was that of a vague inability to see. Objects seemed far away and strange. He referred to them as out of focus but further described them as unreal. Returning home he became lost in an oft-frequented subway station. He lost his way similarly coming home from a store. But in each instance his vision "cleared" when a friend turned him in the correct direction.

He drove his car to the service station without difficulty but once there he was unable to find the knobs on the dashboard. The attendant accused him of being drunk.

Examination showed a left lower quadrantanopia with initially some sparing of the macula. On attempting to draw a floor plan of his house he neglected the left side. His depiction of a clock showed a disarray of figures on the left side and his attempted portrayal of a human face showed a predominantly left-sided distortion with curious misplacement of the ears (fig. 10). Yet there was no dressing apraxia.

The presumptive diagnosis was a thrombosis of the right middle cerebral arteries.

Case 15. A 54-year-old woman who was admitted to the hospital with the chief complaints of headache and some confusion. On examination, she was found to have a left homonymous hemianopia, a defective opticokinetic response on rotation of the field to the right, and a spasticity of gaze to the left. She drew a poor floor plan of her house, with particular neglect of the left side. A clock face was drawn as a mirror image. But especially noteworthy was the fact that she inverted pictures that were handed to her and persisted in holding reading matter upside down (fig. 11). The lesion was presumed to be a vascular accident in the right parietotemporal region.

Dressing apraxia is often the most distressing symptom to the patient and to his family. It is an inability to put on one's clothes properly. More specifically, it is an inability to arrange one's clothes so that they may be put on. The following are some examples in which dressing apraxia was a conspicuous symptom.

Case 16. A 45-year-old man who developed a multitude of symptoms including spinning of en-

vironment, spells of weakness (helped by whiskey!), and alleged black-outs. Early in the course of his illness he became unable to put on his pants or tie his shoes. He missed objects that he reached for and burned himself several times when he tried to light a cigarette. Later he developed convulsive seizures with turning of his eyes to the left.

Examination showed a left hemianopia with sparing of the macula and a defective opticokinetic response on rotation of the field to the patient's right. Craniotomy revealed a right parieto-occipital glioblastoma.

Case 17. An 81-year-old man whose first symptom was dropping of a glass from his left hand. The patient then became aware that the left hand was clumsy and numb. In addition he was unable to put on a wrapper or to undress himself. Most annoying to him was the inability to insert a dental bridge in his mouth.

On examination he was bright and well oriented despite the profound dressing apraxia. He had a left hemianopia and a partial defect in the right field. Yet he persistently denied any difficulty with vision even when it was pointed out to him that he could not see throughout a large part of his field (Anton's syndrome).

Case 18. A 68-year-old man, who failed to appear for breakfast one morning, was found by his daughter in his bedroom unable to get his clothes on. The bureau drawers were open and various articles of clothing were scattered about the room.

The patient was brought to the hospital where he was found to have a left homonymous hemianopia and a dressing apraxia. The difficulty with dressing appeared to be predominantly left sided. Thus he would put his right arm in the sleeve of a jacket but would not realize that the jacket might be reversed or upside-down. Nor did he make any attempt to put his left arm in a sleeve hole. The patient seemed reasonably intelligent but language barriers prevented any penetrating evaluation.

Auto accidents are common with lesions in the right parietotemporal area. Without definite accidents it is common to elicit the story of "driving all over the road." It does not seem to be merely the hemianopia which causes the accident for no such story is so frequently elicited with patients having a left sided lesion or with hemianopias of tract origin. Rather the proneness to accidents would seem to be related to the disorientation in spatial perception.

The following are cases of lesions in the right parietotemporal area which, in addition to some of those previously cited, illustrate the association with auto accidents.

Case 19. A 53-year-old man who had been having headaches for one year. One day he called his wife



Fig. 11 (Cogan). Upside-down reading in a patient with a lesion of the nondominant hemisphere (Case 15).

saying he was having severe pain in the region of a dental extraction. Later he called again saying he was very sick and was coming home. On the way he had an auto accident, the details of which he could not recall, and spent the subsequent two hours wandering about the city unable to find either his office or his home. When he was picked up he was taken to his home and later transferred to the hospital where he was found to have a left hemianopia and severe hypertension. He died a few days later and was found to have a cerebral hemorrhage in the right parietal area and a dissecting aneurysm of the aorta.

Case 20. A 59-year-old man whose initial symptom was slight memory loss. He was then observed to lose his way and allegedly "drove all over the road." One day he spent several hours driving a quarter of a mile from his house to his office. He began running into things and damaged his car on several occasions. Eventually he developed headache in the "back of his eyes" and across the forehead on the right and complained of seeing balls of light moving forward in a constant stream.

The chief abnormality on neuro-ophthalmic examination was a left homonymous hemianopia. X-ray film of the chest revealed a probable bronchogenic carcinoma. The patient died a few months later. Autopsy revealed a metastatic tumor in the right temporoparietal area.

Case 21. A 57-year-old optician was admitted to the hospital with the presumptive diagnosis of brain tumor.

His chief complaint was that of weakness in his

left arm and leg, followed by right frontal headache. This had begun precipitously five days previously and subsequently improved somewhat. When describing his difficulty he observed that his "left arm felt as if it belonged to a dead person; was not part of me."

Additional history obtained from the patient's wife was that for the previous month or two his automobile driving had become extraordinarily hazardous. He unwittingly drove on the extreme left-hand side of the road forcing several oncoming cars to pass on his right side. He had always been a good driver previously and was apparently unaware of this recent erratic behavior.

Examination of the eyes showed an asymmetric, predominantly left homonymous hemianopia and an absence of the optokinetic response on moving the field to the patient's right. Except for a minimal anisocoria and an amblyopia of the left eye dating from childhood, the eyes were otherwise normal. However, it was noteworthy that the patient persistently projected an object in the left field toward the midline. Thus when an object was placed in the seeing part of his left field and he was asked to point to it he invariably underestimated its position. This occurred irrespective of which hand was used for the projection and did not occur with objects in the right field.

Neurologic examination revealed nothing of note, aside from the eyes and a suggestion of astereognosia on the left. The alleged feeling of weakness and nonbelongingness on the left side was not borne out by any objective finding of weakness or reflex changes on the left side. A right carotid arteriogram and pneumoencephalogram were also noninformative. The electroencephalogram suggested some depression of activity on the entire right side. The total protein of the spinal fluid was 92 mg. percent.

The patient was discharged with the presumptive diagnosis of right middle cerebral artery thrombosis. Information from the patient's wife indicated that he died about three years later. No autopsy

was done but the death certificate recorded "cardiac failure and status asthmaticus."

DISCUSSION AND SUMMARY

The foregoing has been an illustrated presentation of the signs and symptoms associated with lesions in the parietotemporal portions of the brain. These areas have important ocular motor and visual cognitive functions and warrant more attention in the ophthalmologic literature than has been accorded them. Some are relatively objective signs and occur with lesions in either hemisphere. Such are the hemianopias, the disturbances of the optokinetic response, and the spasticity of conjugate gaze. Others are more subtle and tend to be associated with lesions in one or the other hemisphere. Such symptoms are the defects in interpretation of written symbols, as occurs with lesions in the dominant hemisphere, or faulty recognition of spatial relationships, as occurs with lesions in the nondominant hemisphere. These and the associated neurologic deficits are important correlatives of hemianopia.

243 Charles Street (14).

The patients cited in this report were seen by me either privately or in conjunction with the Neurologic Service at the Massachusetts General Hospital. I am particularly indebted to Dr. I. H. Zieper, former resident in neurology, for Figure 11, and to the Department of Neuropathology for photographs of the brain specimens.

THE ROLE OF THE PIGMENT EPITHELIUM IN OCULAR PATHOLOGY*

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The opportunity to participate actively in these annual ceremonies to commemorate Mark J. Schoenberg is an extremely pleasant one for me. I know of no one, to my mind,

who so epitomized a true scientist and an ideal clinical investigator as Dr. Schoenberg. He was honest, contagiously enthusiastic, eager to push back clinical frontiers not for his own glorification but for ophthalmology, and I am positive for the benefit of mankind. He was possessed as few are of real altruism, especially toward the younger men in our profession. I shall cite an example. He was the first American, so far as I know, to visit

*This paper was delivered as the Schoenberg Lecture for the Eye Section of the New York Academy of Medicine, December 7, 1959. This lecture is sponsored by the New York Society for the Prevention of Blindness and the New York Society for Clinical Ophthalmology.

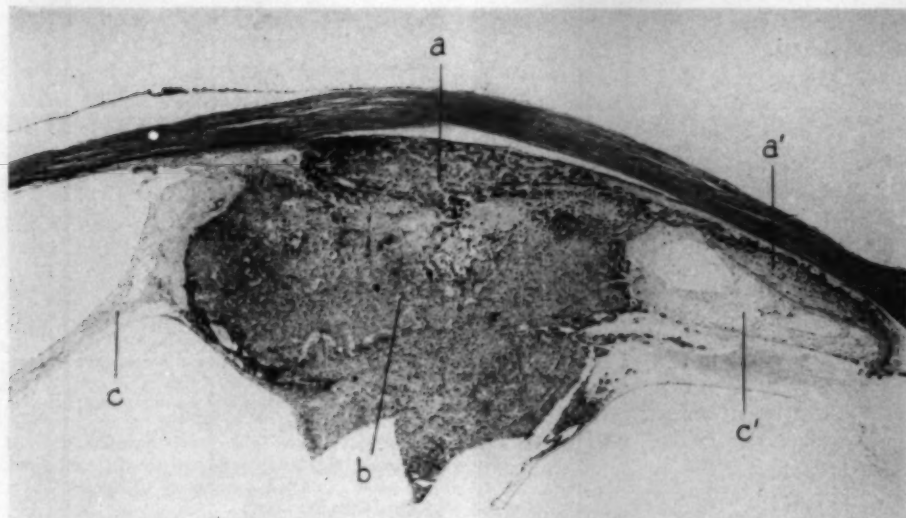


Fig. 1 (Reese). *Hyperplasia of the pigment epithelium of the retina.*

A woman, aged 56 years, had attacks of "sore eyes" at about the age of five to six years. After this the vision was always poor. For five years both eyes were painful and the vision became further reduced with ultimate blindness. There was severe pain in the left eye requiring enucleation.

Clinical examination of the left eye showed dilatation of the episcleral vessels and a tension of 70 mm. Hg (McLean). There was a corneal pannus which prevented a view of the interior. The right eye was slightly congested, the cornea showed opacities, there were posterior synechias, and the tension was 38 mm. Hg (McLean).

This photomicrograph is from the left eye and shows marked hyperplasia of the pigment epithelium. At (a) and (a') the hyperplasia still resembles the mother cells but at (b) it takes the form of a large plaque of metaplastic fibrous tissue interspersed with pigment. The complete gliosed and adherent retina is seen at (c) and (c'); elsewhere in the eye there was some bone formation in old scar tissue.

The cornea showed old degenerating scar tissue with calcium deposits; there were peripheral anterior synechias, occlusion of the pupil, and complete glaucomatous cupping of the disc.

The consensus of those who studied this section, including Dr. F. H. Verhoeff, was that this represented a pure hyperplasia of the pigment epithelium into a tumorlike mass. (It is through the courtesy of the Armed Forces Institute of Pathology and Dr. J. G. Johnstone of Charlotte, North Carolina, that this specimen is available. Reproduced from *Tumors of the Eye*, page 62.)

Gonin in Lausanne and learn the technique for treating retinal detachment. When he returned to New York from that mecca he wore the green turban very graciously. I had been practicing ophthalmology only a few years and yet he twice made trips to the New York Eye and Ear Infirmary to help me operate on patients whom I had wanted him to treat. When I think of Mark Schoenberg, I immediately have the mental picture of a kind, warm, smiling, gracious and engaging friend asking me why I did, said, or wrote, something which he thought was wrong. Now what better friend could one have?

My subject this evening is the pigment epithelium and the role it plays in ocular pathology. It is my feeling that this pigment epithelium has not received due recognition. It is a roguish tissue which has been trying, to little avail, to get into the ophthalmologic act by annoying us, duping us, and cajoling us. It annoys us by intruding itself into situations where it is not wanted (by growing boundlessly in tissue cultures, by becoming neoplastic when we least expect it, by destroying central vision to make our old age even more trying); it dupes us into making incorrect diagnoses (by masquerading as a



Fig. 2 (Reese). Hyperplasia of the pigment epithelium of the retina.

Below the disc is a highly elevated black stalk of tissue which protrudes so far forward in the vitreous that it casts a shadow from the ophthalmoscope light. Around this focus of proliferated epithelium is an old area of inactive choroiditis. This is interpreted as an instance of hyperplasia of the pigment epithelium secondary to a choroiditis.

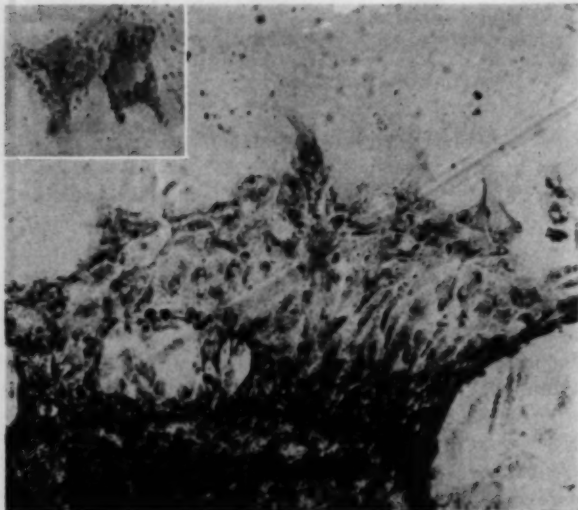


Fig. 4 (Reese). Culture of pigment epithelium.

A tissue culture showing the florid growth (17 days) of the pigment epithelium in a normal eye. The culture was taken of the choroid but the pigment epithelium has outstripped all other growth. The insert shows a high-power view of two cells. (Jenner-Giemsa stain.)



Fig. 3 (Reese). Hyperplasia of the pigment epithelium of the retina.

A primary hyperplasia of the pigment epithelium of the retina adjacent to the disc in an otherwise normal eye. There is marked drusenlike material throughout the lesion produced by the epithelium. The lesion simulated a malignant melanoma. (Lent by Dr. James W. May.)

melanoma); and it cajoles us by playing an important role in the successful outcome of some of our surgery (by closing holes in detachments of the retina, by promoting filtration in glaucoma).

Few, if any, tissues in the body have such versatility manifested by the following four characteristics:

1. It proliferates upon the slightest provo-

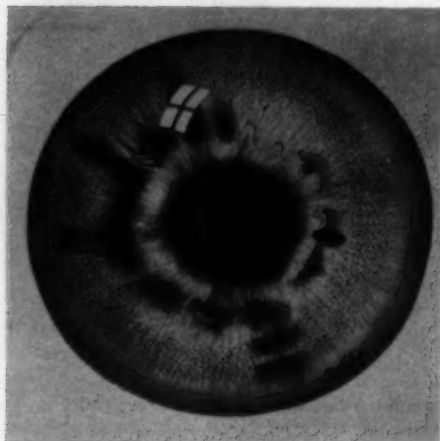


Fig. 5 (Reese). Migration and proliferation of pigment epithelial cells in glaucoma.

The left iris of a man with primary glaucoma to show the pigment dust over the iris surface representing migration of pigment epithelial cells through the stroma of the iris (clump cells) and a large plaque, or freckle, of proliferated pigment-epithelium cells on the anterior surface of the iris in the area of the collarette at the 3-o'clock position.

cation. The proliferative cells resemble the mother cell with all gradations to a metaplastic fibrous tissue. Under seemingly slight provocation, large plaques, or even tumefactions, appear which resemble neoplasms

Fig. 6 (Reese). Hyperplasia of the pigment epithelium of the iris.

A woman, aged 35 years, had noted a black spot on the iris of the right eye for an indefinite length of time. Due to the fact that the patient's father had a malignant melanoma of the iris and ciliary body which required an enucleation, she became unduly apprehensive about the spot and wanted it excised. The clinical diagnosis was a benign melanoma (hyperplasia) of the iris arising from the pigment epithelium. This was confirmed by histologic study.

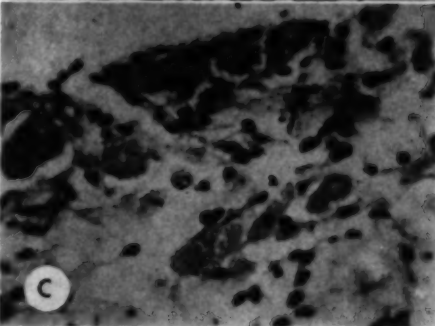
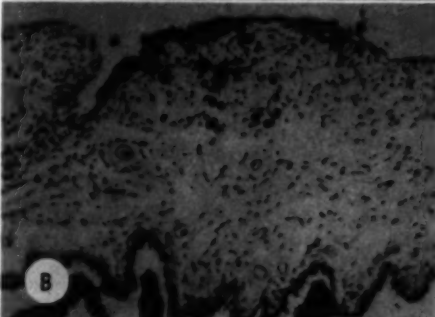
(A) A flat plaque of proliferated pigment epithelium on the anterior surface of the iris simulating a true melanoma in an otherwise normal eye.

(B) A section through this lesion, showing the accumulation and proliferation of pigment epithelial cells on the anterior surface, and an aggregate of these cells in the adjacent stroma. In serial sections the pigment epithelial cells could be traced from the pigment epithelial layer through the stroma to the lesion on the anterior surface.

(C) A depigmented section of the lesion showing the cells to be pigment epithelium.

(figs. 1, 2, and 3). This seems to be the only intraocular tissue, excepting supporting tissue, which can reproduce its kind. In tissue culture work,¹ it might be called the weed among the tissues because it outstrips all other growth. Therefore, an attempt to grow other tissue is often frustrated by the tremendous growth potential of this epithelium (fig. 4).

2. It migrates. The pigment epithelium migrates into the iris, particularly in the sphincter area, as clump cells, or throughout the iris stroma as pigment dust in primary glaucoma.



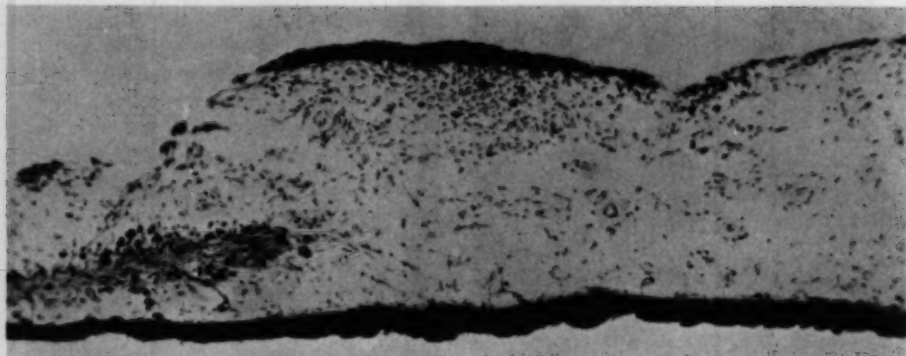


Fig. 7 (Reese). *Pigment epithelial freckle of iris.*

A freckle of the iris due to migration of pigment epithelial cells (clump cells) through the stroma of the iris to the anterior surface where they proliferate. The epithelial cells can be traced from the sphincter muscle around which are many clump cells through the stroma to the freckle on the anterior surface. Depigmented sections show that the freckle is composed of pigment epithelium. (This is a normal eye which was removed when the orbit was exenterated because of a meningioma.)

(figs. 5, 6, and 7). If there is a break in the external limiting layer of the retina, the pigment epithelium, because of its phototaxic properties, migrates into the retina. This situation is encountered in retinitis pigmentosa

as well as other conditions. Also, apparently the epithelium may extend quite far into the optic disc from its termination at the disc margin.

3. It seeds. Disseminated or transplanted epithelial cells may remain viable and even grow. As discussed later, these seeds are seen on the posterior surface of the cornea and on the anterior surface of the iris (figs. 8, 9, and 10).

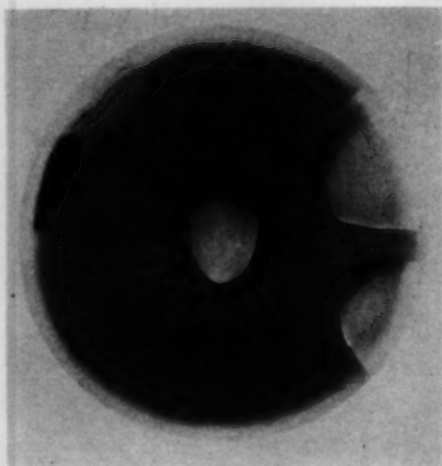


Fig. 8 (Reese). *Seeding and hyperplasia of the pigment epithelium following surgery.*

Following two operations for primary glaucoma there occurred some seeding of the pigment epithelium on the anterior surface of the iris between the 6- and 7-o'clock positions. The epithelium has proliferated and formed a rather large plaque of black tissue.



Fig. 9 (Reese). *Seeding and proliferation of pigment epithelium on the posterior surface of the cornea following cataract extraction.*

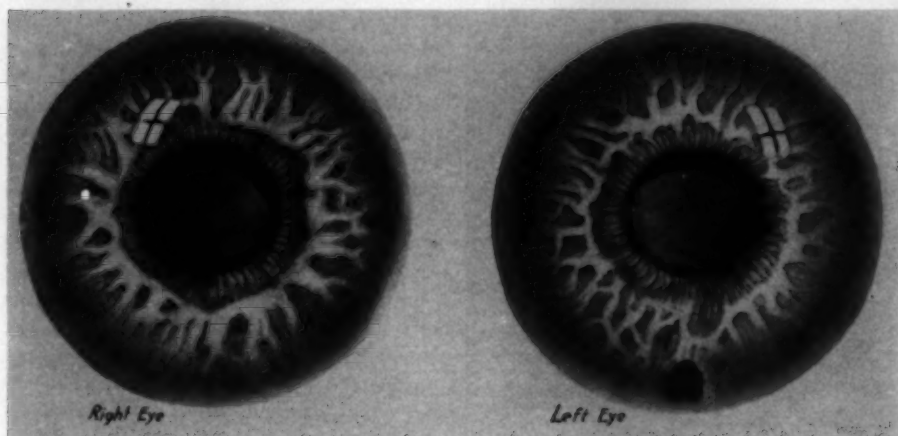


Fig. 10 (Reese). *A free and proliferated pigmented excrescence on the surface of the iris of the left eye. Atavistic pigment changes of the pupillary margin.*

A 58-year-old man sought advice because of a black spot on the iris of the left eye. Examination showed an elevated black nodule of pigment at the 6-o'clock position, lying on and growing over the iris surface. This lesion showed no evidence of being cystic. There were rather marked excrescences of pigment at the pupillary margin of each eye, mainly above but to a lesser extent below. Both eyes were otherwise normal. There was no history of trauma or the use of any local medication in the eye. This was interpreted as representing congenital atavistic excrescences of the pigment epithelium. One of these excrescences became dislodged and implanted itself in the dependent portion of the angle where it apparently proliferated.

4. It secretes. The epithelium produces a cuticular product which is homogeneous and stains with eosin. This is seen normally as the inner layer of the lamina vitrea and as excrescences or drusen of this layer in senescence. Hyperplasias and tumors arising from this epithelium also manifest the product of this secretory function (figs. 3 and 11). It is my belief, based on substantial evidence, that this property of the pigment epithelium may be responsible for senile macular degeneration. The epithelium, by laying down this cuticular product and thereby thickening the lamina vitrea, impairs the circulation of the macula which is dependent on the choroid for its nutrition. In this way, a senile macular degeneration is produced on the basis of anoxia.

These just-mentioned characteristics of this tissue will be encountered over and over in the ensuing discussion.

This epithelium will now be discussed under the headings of hyperplasia, tumors, and

cysts as they are seen in the retina, ciliary body, and iris.

A. RETINA

1. HYPERPLASIA

a. Congenital

Congenital hyperplasia of the retinal pigment epithelium is seen clinically as a flat, jet-black area sometimes mistaken for a malignant melanoma (fig. 12).

b. Acquired

Secondary to inflammation. It is common in our clinical work to observe the proliferated epithelium as a result of a choroiditis. In the acute stage, the site of the inflammation may be seen as an indistinct gray zone with or without a collarette of hemorrhage. The dark color here seems to be secondary to the changes in the pigment epithelium. As the process regresses the choroiditis usually is lethal to the epithelium overlying the central part of the lesion and stimulating to the pe-

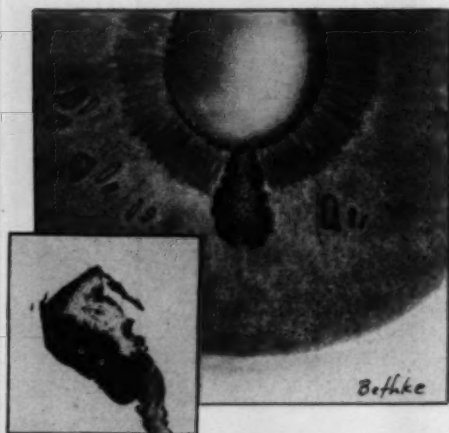


Fig. 11 (Reese). *Hyperplasia (adenoma) of the pigment epithelium of the iris.*

A woman, aged 43 years, noted this pigmented lesion of the iris for the first time three months prior to examination. She felt it had become progressively larger. The growth had a rather papillomatous or mulberry appearance.

Sections of the tumor (insert) show that it is continuous with the normal pigment epithelium on the posterior surface (partially desquamated in preparation of the sections). Blood vessels course through this tumor but no actual stroma is seen. There is some hyaloid material (cuticular product) consistent with most lesions of the pigment epithelium. The tumor cells are shown by bleached sections to be epithelium growing in an adenomatous arrangement.

ripheral part. This leads to the central white area (barring of the sclera) surrounded by a black collarette or proliferated pigment epithelium. When the response from the chorioiditis is not lethal but stimulating, then the proliferated pigment epithelium may be seen over the entire site of the lesion.

It is not uncommon to find in eyes, blind from injury or inflammation, large plaques of proliferated epithelium manifested as metaplastic fibrous tissue. Sometimes these plaques form tremendous tumefactions and even pose a problem in clinical and histologic differential diagnosis between hyperplasia and neoplasia. This inordinate amount of proliferation of the pigment epithelium is usually seen in blind eyes and, therefore, frequently not seen clinically but only micro-

scopically (fig. 1). Sometimes, however, this massive proliferation may be seen in eyes in which the interior is visible (fig. 2) and then the clinical problem arises as to whether or not we are dealing with a malignant melanoma.

Associated with macular degeneration. It is my feeling that in some or all of the instances of senile macular degeneration the pigment epithelium is the culprit. As a manifestation of senescence, the epithelium leads to a thickening of the inner layer of the lamina vitrea and this impairs the blood supply to the macular region which is dependent on the choroid. The dark color which may be present in disciform degeneration is due not only to hematogenous pigment but also to the proliferation of the epithelium. In this way a melanoma is simulated.

Following surgery. The repair tissue which results from the application of scleral or choroidal diathermy, and which seals the hole as well as the retina to the underlying choroid, emanates from the pigment epithelium. Therefore, it is to this epithelium that we owe our debt of gratitude for our ability to reattach the retina through surgery.

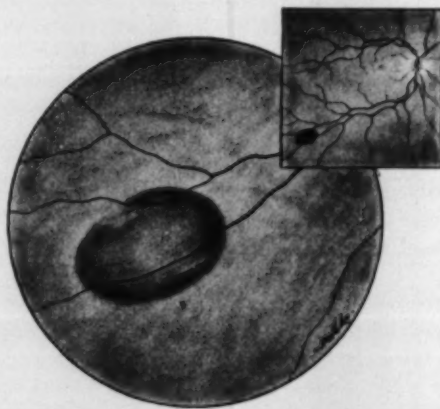


Fig. 12 (Reese). *Congenital hyperplasia of the pigment epithelium of the retina.*

This manifests itself as a flat, dark-gray lesion. The insert shows the location of the pigmented area in relation to the disc. (Reese, A. B. and Jones, I. S.: Benign melanomas of the retinal pigment epithelium. *Am. J. Ophth.*, 42:207-212, 1956.)

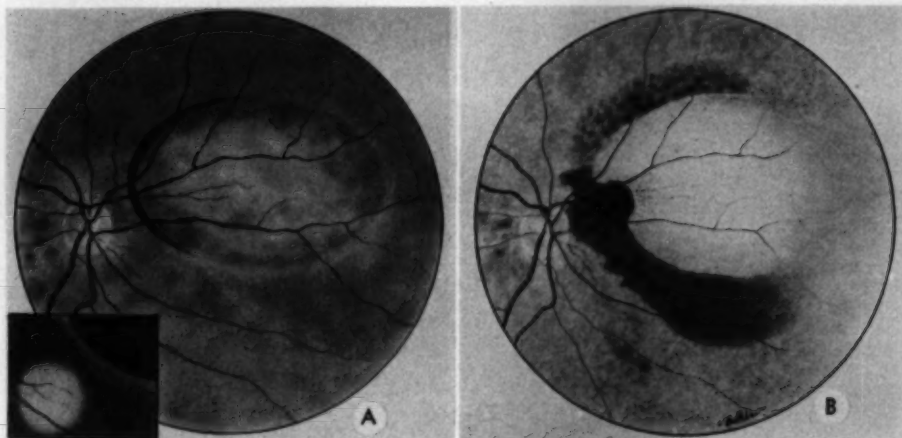


Fig. 13 (Reese). *A* hematoma of the pigment epithelium in the macular area.

A woman, aged 60 years, noticed a sudden disturbance of vision of the right eye. The recorded vision, however, was 20/20. A similar episode occurred in the left eye a year ago when a diagnosis of malignant melanoma of the choroid was made and an enucleation was done. Sections of the eye were obtained and studied. They showed a hematoma of the pigment epithelium.

(A) The appearance at the first examination. The lesion resembled a melanoma in every detail except for a narrow collateral hemorrhage at one border. The insert shows the dark border by retroillumination.

(B) The appearance 19 days later. The picture has changed so hemorrhage, pigment proliferation, and color make the diagnosis obvious.

From a choroidal tumor. The epithelium overlying a choroidal melanoma or hemangioma may proliferate, desquamate, and migrate so that it will be seen not only over the tumor but elsewhere.

From trauma. Proliferation of the epithelium may be a feature in lesions of the fundus from contusion (retinitis sclopetaria, ruptures of the retina and choroid).

c. Primary hyperplasia

A primary hyperplasia of the pigment epithelium may occur in the sense that no provocation for the proliferation is apparent. This is a group which seems to have been too little appreciated in the past. The instances that have encountered have been seen as an elevated localized mass at some site on or around the disc (fig. 3). Theobald² has reported two such cases in which the clinical picture suggested not only melanoma but also an angiomatous process. Another case belonging to this group has been reported by Rein.³

2. TUMORS

The large plaques of hyperplastic epithelium seen sometimes in blind eyes which have been the seat of inflammation may eventually become true neoplasms and even carcinomatous. There are a number of such cases reported in the literature (Fuchs,⁴ Stow,⁵ Greer⁶). In addition, primary carcinomas of the pigment epithelium may occur in eyes with no evidence of previous pathology (Fair,⁷ Cury, Lucic, and Irvine⁸).

3. CYSTS

There are no cysts of the pigment epithelium of the retina, so far as I know, unless the blood cysts or hematomas occurring in the macular region are considered in this category. These hematomas, however, comprise an important group because when they first occur they can simulate a melanoma more closely than any other fundus lesion I know (fig. 13-A and B). The patient experiences a sudden reduction in vision which may have been coincident with a coughing, sneezing, or

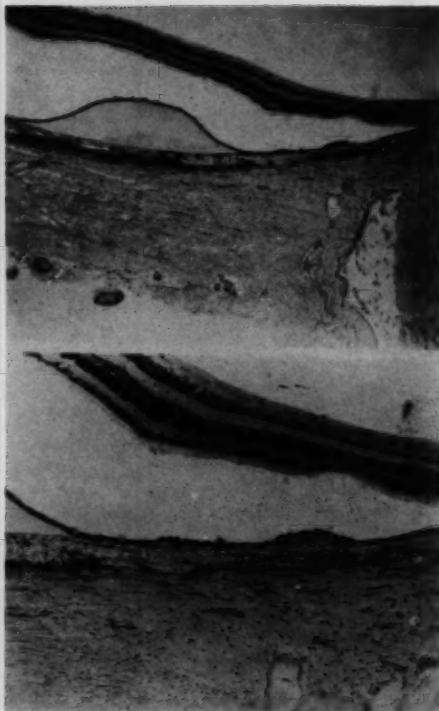


Fig. 14 (Reese). Hematoma under pigment epithelium of macula.

In the section above there is a hematoma in the macular area under the pigment epithelium. The lower section shows a somewhat higher magnification of the vascular membrane which interposes itself between the pigment epithelium and the lamina vitrea and from which the hematoma occurred.

vomiting attack. The site of the lesion is not necessarily in the macula proper, but may be in the extramacular regions. The only details not consistent with a melanoma are the presence of some degree of hemorrhage around the periphery of the lesion and relatively good vision. This hemorrhage under the pigment epithelium comes from a thin, vascular layer which interposes itself for some unknown reason between the pigment epithelium and the lamina vitrea (fig. 14). Many eyes with such macular hematomas have been removed because the condition had been diagnosed malignant melanoma. The simulation of a melanoma is greatest when the lesion

first occurs and when the patient naturally first consults the ophthalmologist. In the course of weeks the picture changes rapidly so that hemorrhage dominates the clinical appearance and the true nature of the condition can be more easily appreciated.

B. CILIARY BODY

The ciliary body is covered on the inner surface by two layers of epithelium: the inner is nonpigmented and the outer is pigmented. There is justification, however, for treating these two layers as one. In pathologic processes, as well as in otherwise normal eyes, the inner layer may be pigmented. Also, situations occur where the pigmented layer participates in the formation of a lesion presenting itself primarily in the nonpigmented layer and vice versa, so that a sharp distinction between these two layers is not justified.

1. HYPERPLASIA

a. Congenital

Congenital hyperplasia no doubt occurs but we have no occasion to recognize it clinically and, so far as I know, it has never been appreciated microscopically.

b. Acquired

Acquired hyperplasias of these epithelial layers occur as a response to severe inflammatory processes and just as in the retina the plaques of proliferated epithelium may be quite large.

2. TUMORS

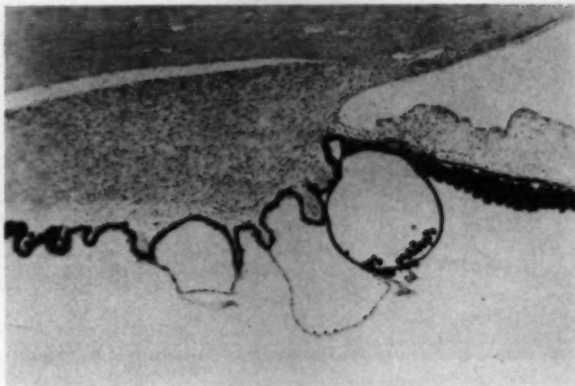
The following types of true neoplasms of the ciliary epithelium occur: (1) benign epithelioma (adenoma); (2) malignant epithelioma; (3) medullo-epithelioma consisting of (a) the embryonal type (dictyoma) and (b) the adult type.

3. CYSTS

Intraepithelial cysts of the ciliary body are frequently seen microscopically but seldom are they large enough to become a clinical problem. These intraepithelial cysts result

Fig. 15 (Reese). *Intraepithelial cysts of the iris and ciliary body.*

An anterior sector of an eye normal except for a relatively small malignant melanoma of the posterior choroid. In addition to two intraepithelial cysts of the ciliary body there is a pedunculated pigment epithelial cyst with free pigment epithelial cells in it at the base of the iris. It is probably such a cyst that sometimes becomes detached and is seen free in the anterior chamber, as shown in Figure 16.



from a separation of the nonpigmented from the pigmented epithelium. These two layers of epithelium are poorly united throughout the eye. Detachments of the retina occur because of this poor union and similarly in the ciliary body and, as later we will see in the iris, these two layers separate to form the so-called intraepithelial cyst. In the ciliary body this is particularly prone to occur at the base of the iris (fig. 15). When their location is at this site and they are sufficiently large, they may push the root of the iris forward sufficiently to lead the clinician to wonder if there is a tumor responsible. Through the dilated pupil, usually one or more globular masses are seen in the ciliary body. It seems likely that the free pigment epithelial cyst sometimes seen in the anterior chamber (fig. 16) may sometimes represent a detached intraepithelial cyst from the root of the iris (fig. 15).

C. IRIS

1. HYPERPLASIA

a. Congenital

In the Ungulata and particularly in the horse, their oval pupils show at the margins above and below rather large excrescences of the pigment epithelium. In man, such lesions appear occasionally and no doubt should be viewed as atavistic progonomas (fig. 10). In man, these excrescences may detach and lie

on the surface of the iris in the dependent portion of the filtration angle. Such an implant may enlarge and simulate a melanoma (fig. 10).

Also in a congenital coloboma of the iris the pigment epithelium may form large excrescences at the margin of the coloboma and even partially or totally fill the colobomatous area.

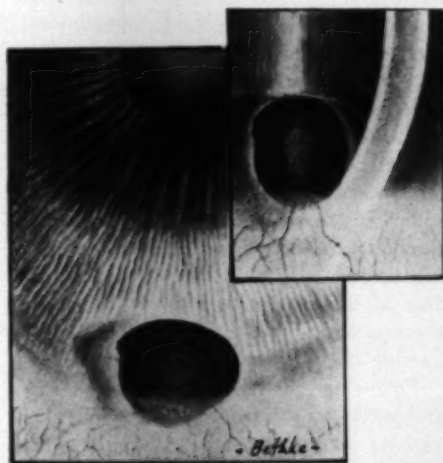
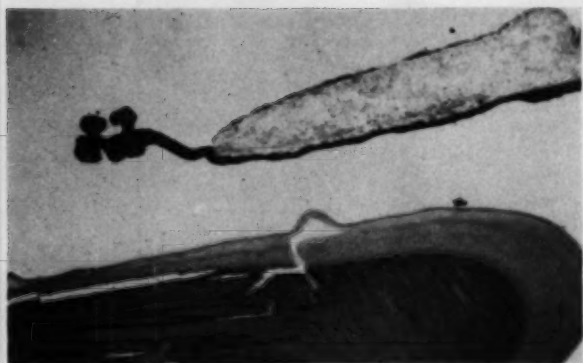


Fig. 16 (Reese). *Cyst of pigment epithelium in the anterior chamber.*

A free cyst of the pigment epithelium is in the dependent portion of the anterior chamber. The cyst moved with the movement of the head. The insert is the appearance with the slitlamp to show the transmission of light and its location in the angle. This occurred in an otherwise normal eye.



b. *Acquired*

This is commonly seen following inflammation of the iris when the pigment epithelium may extend onto the anterior lens capsule. Also, following an uneventful intracapsular (Radnot⁹) or extracapsular (Brueckner¹⁰) cataract extraction, even with the usual postoperative reaction, the pigment epithelium may proliferate across the entire pupillary area. This proliferated pigment epithelium may reduce the vision sufficiently to warrant a discission. In Brueckner's case the pupillary area was so black that the question of a melanoma arose. Atkinson¹¹ has called attention to the fact that flecks of pigment epithelium abraded at the time of the cataract extraction may lodge on the posterior surface of the cornea and proliferate sufficiently to impair vision seriously (fig. 9). Similar flecks of pigment epithelium following surgery may lodge on the anterior surface of the iris and proliferate to simulate a melanoma (fig. 8). The same lesions occurring after surgery may follow trauma.

Following the use of strong miotics, and particularly di-isopropyl-fluorophosphate (DFP), excrescences of the pigment epithelium may be quite marked around the pupillary margin. Secondary cystic changes may accompany the proliferation. Christensen¹² has reported a case of a child treated with DFP with proliferation and cystic changes so marked that an ophthalmologist

Fig. 17 (Reese). *Hyperplasia of the pigment epithelium of the iris.*

Proliferation of the pigment epithelium at the pupillary margin following prolonged use of di-isopropyl-fluorophosphate (DFP). The clinical picture was confused with melanoma and led to enucleation. (Lent by Dr. Leonard Christensen; reported in *Arch. Ophth.*, 55:666-675, 1956. The histopathology of iris changes induced by miotics.)

thought a melanoma of the iris was present and enucleated the eye (fig. 17). Swan¹³ reported a case in which one of the nodules seeded on the iris surface, and another case in which one of the cystic nodules became free and deposited itself in the dependent portion of the angle and enlarged.

I feel that the earliest demonstrable organic change in an eye with primary glaucoma is the migration of pigment epithelium through the iris stroma. Clinically, this is seen as pigment dust over the surface of the iris (fig. 5) and as pigment deposits on the posterior surface of the cornea. Unappreciated is the fact that sometimes these migrating pigment epithelial cells, after they reach the anterior surface of the iris, may proliferate and produce a freckle (fig. 5). These freckles from the pigment epithelium have a velvety jet-black appearance and are prone to occur in the region of the collarette.

Furthermore, in old glaucomatous eyes with ectropion uvea around the pupillary margin of a fixed dilated pupil, the ectropion of the pigment epithelium may extend at one or more sites along the iris surface as a sheet of black pigment.

There is still another type of hyperplasia which is probably acquired. This occurs at the pupillary margin as a localized extension of the pigment seam onto the anterior surface of the iris (fig. 11). The serrations of the pigment seam may be seen extending

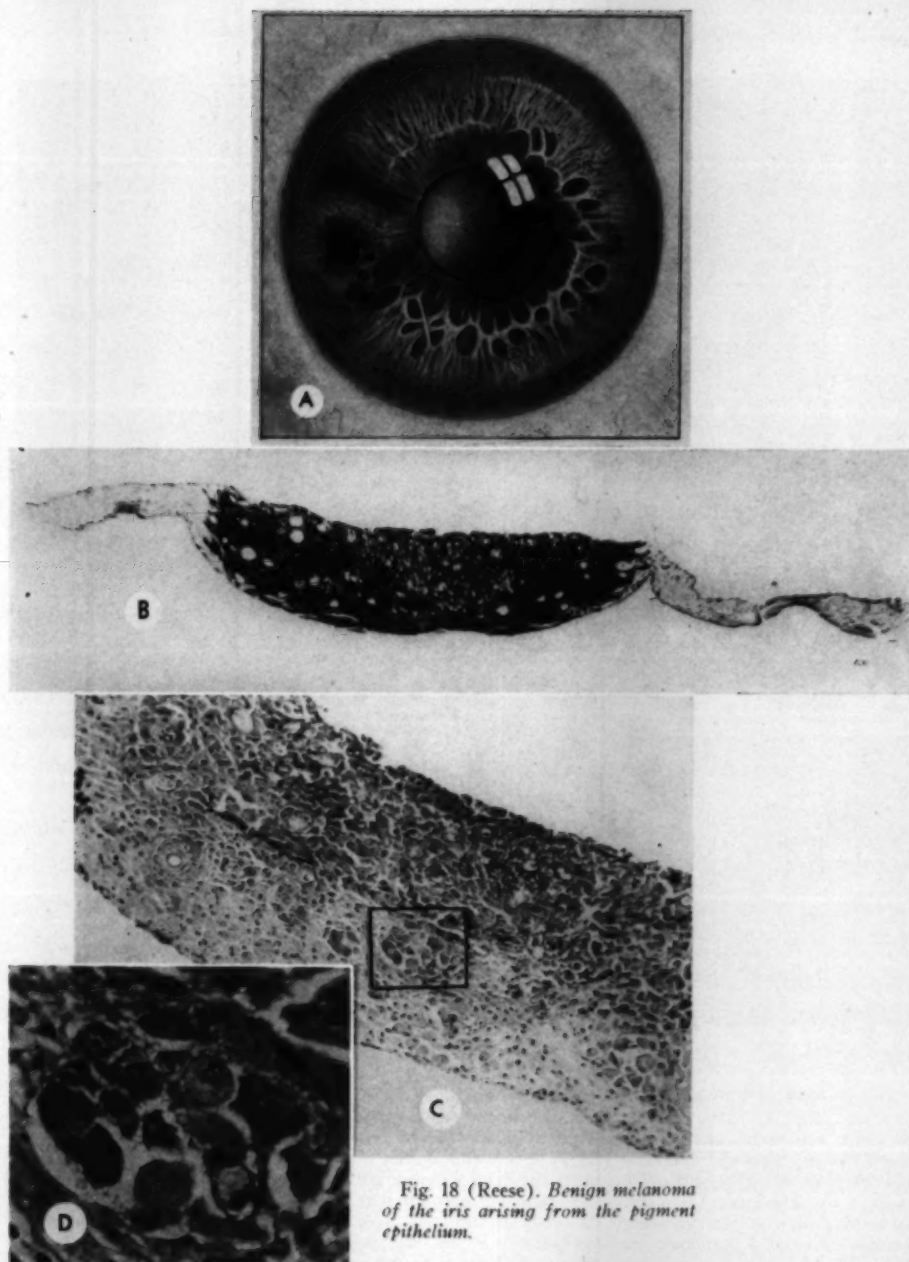


Fig. 18 (Reese). *Benign melanoma of the iris arising from the pigment epithelium.*

A woman, aged 55 years, consulted an ophthalmologist for a routine examination at which time the pigmented lesion of the left iris was noted.

(A) The velvety black part presenting on the anterior surface was only a small portion of the total lesion, or iceberg, the major portion of which was submerged in the stroma. Pigment dust representing migrated pigment epithelial cells (clump cells) is seen over the anterior surface in the region of the collarette as well as over the site of the tumor.

(B) A low-power section through the tumor.

(C) A bleached section of the tumor, showing it to be composed of pigment epithelial cells.

(D) A high-power view of (C).

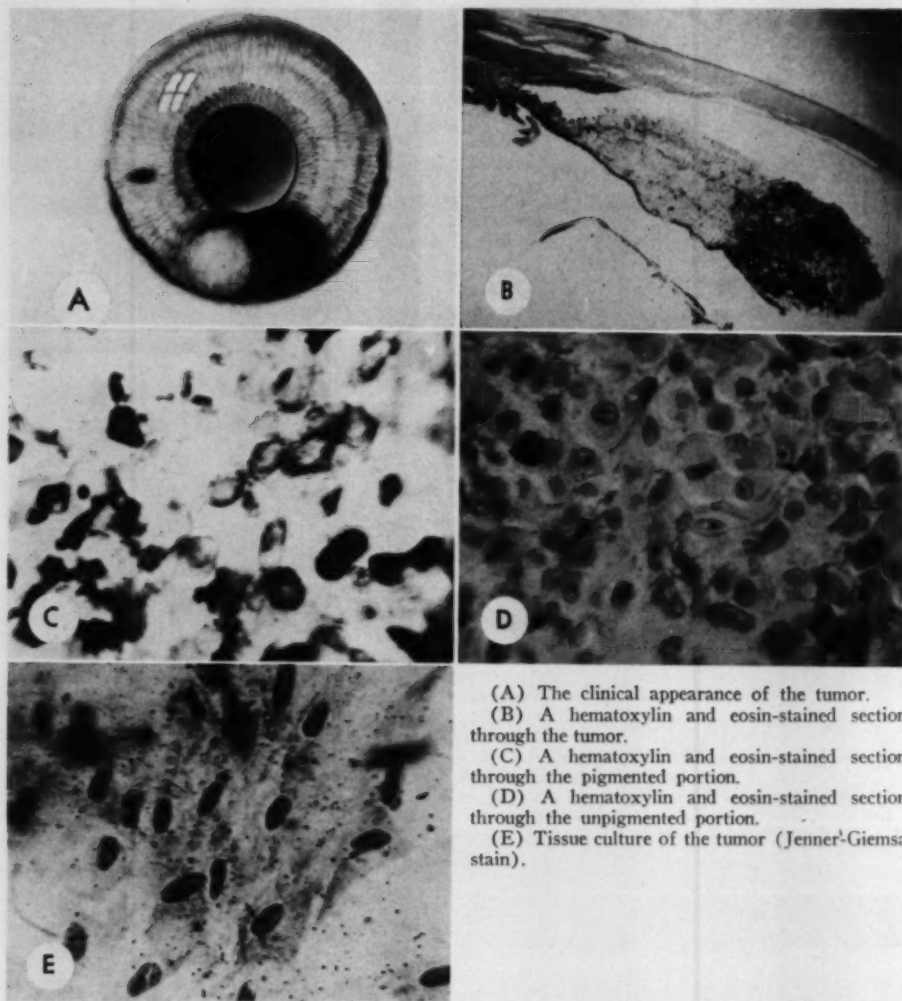


Fig. 19 (Reese). *Carcinoma of the pigment epithelium of the iris.*

A man, aged 65 years, noted a black spot on the right eye one week before he consulted an ophthalmologist. The vision was 4/200 and the tension was 62 mm. Hg with a Schiötz tonometer. There was a black elevated mass with a central grayish area in the anterior chamber extending from the 4- to 7-o'clock positions. From the 2- to 4-o'clock and from 7- to 9-o'clock positions, there was pigmented tissue in the angle (A). The clinical diagnosis was malignant melanoma of the iris. The patient died eight months later of generalized carcinomatosis. A study of the sections of the lung, liver, and spleen obtained at autopsy revealed a carcinoma probably primary in the lung and unrelated to the carcinoma of the iris. Some of the iris tumor was cultured and the type of growth indicated pigment epithelium (E).

over the surface of the hyperplasia as radiating furrows. These lesions probably could be viewed as benign epitheliomas or adenomas comparable to the ones seen in the ciliary

body. I do not believe this lesion ever becomes malignant (see discussion of tumors).

The role played by the pigment epithelium, however, is not always a villainous one. It

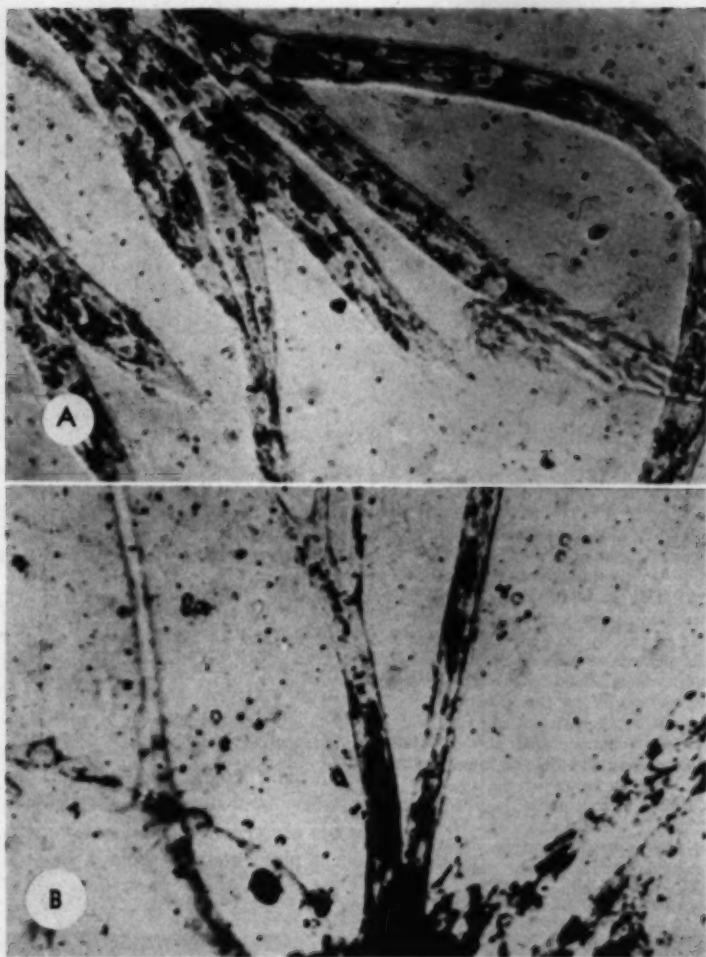


Fig. 20 (Reese). Tissue cultures, showing transitional cells between pigment epithelium and smooth muscle.

(A) Culture of normal iris, 15 days' growth. Living cells. These pigment-bearing cells peculiar to the iris seem to be a rudimentary neuro-ectodermal muscle cell akin to pigment epithelium ($\times 100$). (Normal eye removed when orbit was exenterated because of rhabdomyosarcoma.)

(B) Culture of malignant melanoma of the iris, four days' growth. Living cells. These pigmented cells are interpreted as being neuro-ectodermal muscle cells akin to pigment epithelium and comparable to those found in the cultures of the normal iris (see A).

sometimes has a more charitable role as witnessed in glaucoma surgery where it seems to promote filtration. In the iridencleisis operation the epithelium lines the inside of the iris wick and in this way it seems to encourage filtration.¹⁴

c. Primary

I have just discussed acquired hyperplasias either accompanying or secondary to various conditions. In the sense that no cause is discernible there may be primary hyperplasias.

As a physiologic occurrence, proliferated



Fig. 21 (Reese). Benign melanomas of the pigment epithelium of the iris.

At a routine eye examination two melanomas were noted on the right iris of a man, aged 35 years. In the course of three years these were thought to have enlarged. At the 8- and 8:30-o'clock positions two jet-black melanomas peered through the iris stroma. The stroma around these two sites bulged forward, due apparently to the extension of the tumor into the surrounding stroma. At the 9-o'clock position inside the collarette, and at the 4-o'clock position in the periphery of the iris, were jet-black freckles interpreted as being of the pigment epithelial type. Although no microscopic confirmation has been possible, these tumors have been interpreted as being the iceberg type of melanoma with the pigment epithelium as the stem cell. (Patient of Dr. Benjamin Friedman.)

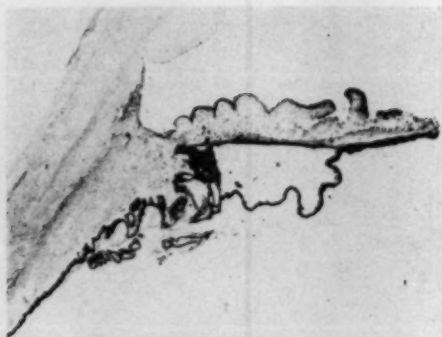


Fig. 22 (Reese). Intraepithelial cyst of iris.

A portion of the anterior sector of the eye to show an intraepithelial cyst which led to enucleation because it simulated a melanoma. (Patient of Dr. Joseph Mandelbaum. Reproduced from *Tumors of the Eye* by Algernon B. Reese, p. 291, fig. 147.)

pigment epithelial cells migrate into the iris stroma as clump cells in the region of the sphincter muscle.

I feel that some of the ordinary freckles of the iris are in fact localized accumulations of migrated pigment epithelial cells which have proliferated along the anterior surface (fig. 7). These are prone to occur in the pupillary third of the iris where the clump cells are normally found but they may be seen anywhere over the iris. The freckles of this origin are velvety black and identical in color to the pigment seam around the pupillary margin. The usual type of so-called freckle is

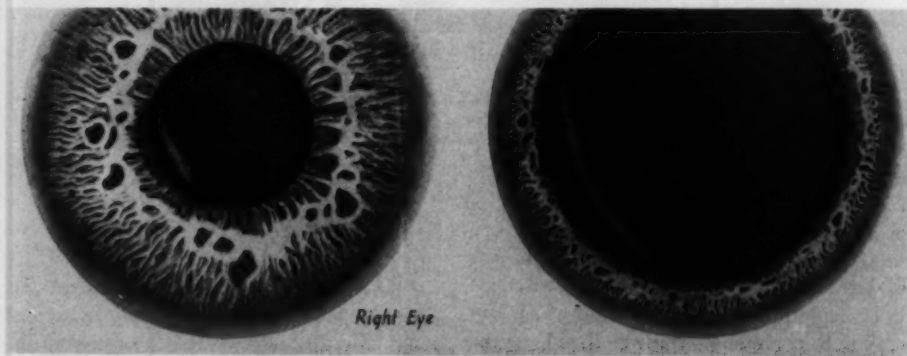


Fig. 23 (Reese). Intraepithelial cyst of the iris. The drawing on the left shows an intraepithelial cyst with the pupil in its normal state. The drawing on the right shows the eversion of the cyst with the pupil dilated.

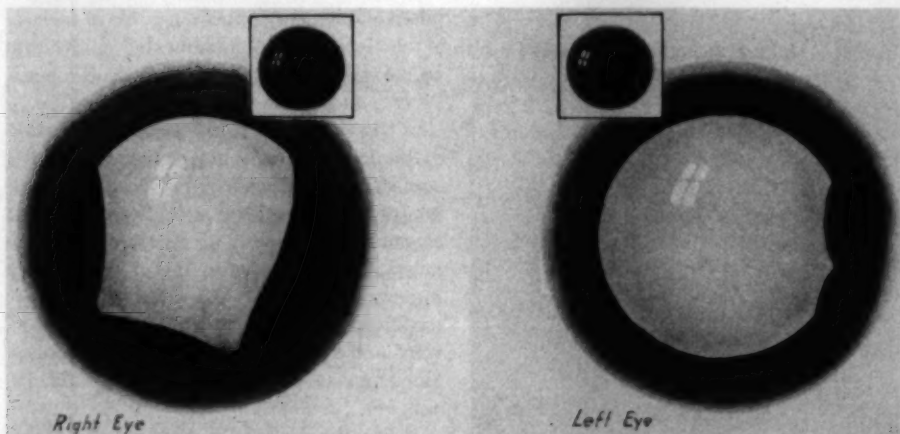


Fig. 24 (Reese). *Bilateral multiple intraepithelial cysts of iris.*

(Right eye) In the normal state of contraction of the iris, shown in the insert, a cyst is barely seen nasally but with the pupil dilated three cysts manifest themselves.

(Left eye) In the normal state of contraction of the iris, shown in the insert, no cysts appear but with the pupil dilated two cysts manifest themselves temporally. (Patient of Dr. Alston Callahan.)

due to a localized thickening of the anterior limiting layer of the iris and, clinically, these are seen as lighter brown lesions. Pigment epithelial cells may migrate from no apparent provocation to the anterior surface of the iris at one site and proliferate over the surface to form a single sheet of black pigment resembling a melanoma (fig. 6).

2. TUMORS

The subject of tumors of the pigment epithelium of the iris is a complicated one. The nonpigmented layer of the ciliary body is continued onto the iris as the pigment epithelium, so from this layer alone in the iris we have the possibility of congenital and acquired medulloepithelioma (diktyoma) as well as benign and malignant tumors (figs. 18 and 19) composed of pigment epithelium.

The pigment epithelium of the ciliary body is continued onto the iris as the dilator muscle so from this layer we have all gradations of tumors from leiomyoma to frank pigment epithelium (figs. 20-A and B) and in the same tumor often these variations in the cytology may be seen. Some authors¹⁸ even question the existence of a true leiomyoma arising from this neurogenous smooth mus-

cle but they feel that most, if not all, of these tumors are really neurinomas.

A benign melanoma of the iris pigment epithelium occurs which has unusual clinical features. Most of the tumor cells lie embedded in the iris stroma and only a small part of the black tumor is viewed bare on the anterior surface of the iris (figs. 18 and 21). So far as I know this iceberg type of iris melanoma is entirely benign. As a matter of fact it may be another instance of a lesion of the pigment epithelium which lies in the lim-

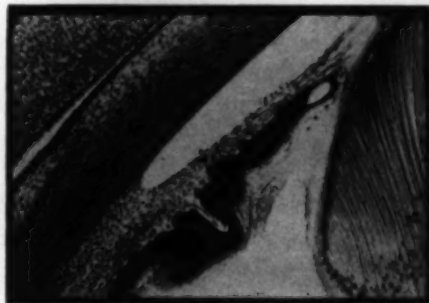


Fig. 25 (Reese). *Marginal ring sinus.* Section of the iris of a 70-mm. human fetus, showing the marginal ring sinus (Szily). (Lent by Dr. George K. Smelser.)

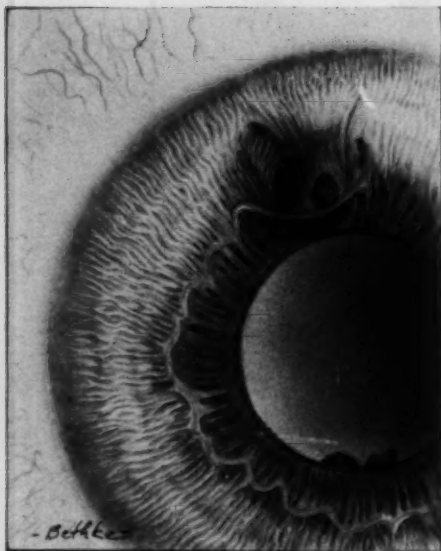


Fig. 26 (Reese). *Pupillary (marginal sinus) cyst of iris.* At the 12-o'clock position there is a cyst which transmitted light. At the 6-o'clock position there are two excrescences of the pigment epithelium (probably potentially cystic).

bal region between hyperplasia and neoplasia. In eyes harboring these tumors there has been no history or sign of inflammation, glaucoma, or trauma. The iris involved may show an unusual number of clump cells seen as pigment dust especially in the region of the collarette and the tumor (fig. 18), or there may be freckles of the pigment epithelium (fig. 21).

Malignant tumors of the iris pigment epithelium do occur. The only one I have seen or know of is shown in Figure 19.

3. Cysts

The types of iris cysts which concern us here are those which stem from the pigment epithelium. It is these that may mimic a melanoma. Two types come in for consideration: the intraepithelial and the pupillary.

a. *Intraepithelial cysts*

In the iris the same layers separate as in the ciliary body to produce these cysts. In the iris the posterior layer of the cyst is com-

posed of pigment epithelium while in the ciliary body it is the nonpigmented epithelium. In the iris, therefore, such cysts have a black surface and do not transilluminate.

When the cyst is in the peripheral portion of the iris, it usually bulges the anterior iris surface forward producing a localized globular protrusion with rarely some pigment changes in the overlying iris stroma due to migration of pigment epithelial cells. When the cyst is located in the central half of the iris there may be no bulging of the iris forward and the cyst is only detected as a black globular mass back of the iris (figs. 22, 23, and 24).

When the pupil is in its natural or contracted state, the cyst is more or less concealed, whereas, when the pupil is dilated, the cyst everts to be seen much more prominently in the pupillary area (fig. 23). Frequently in the normal or contracted state of the pupil such an iris cyst may not be seen at all, or may be seen only at one site around the pupillary margin, but when the pupil is dilated not only does this site become more visible but several other smaller cysts may

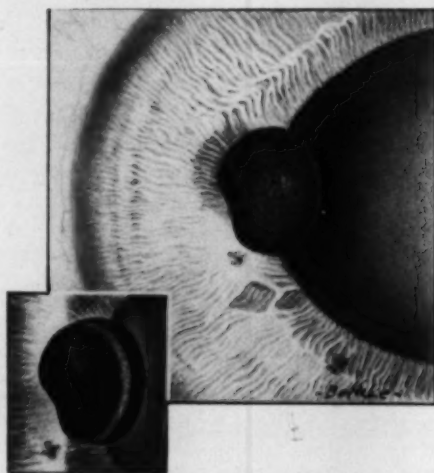


Fig. 27 (Reese). *Pupillary cyst of the iris.*

A man, aged 21 years, had noted a brown spot on his left iris for an indefinite length of time. A dark-brown globular cyst is moored to the left iris nasally at the pupillary margin. The insert shows that a slitlamp beam passes through the cyst.

be seen in the same eye or in both eyes (fig. 24).

Because of the black surface and the failure to transilluminate light these iris cysts are often confused with melanomas of the iris. Important features in the differential diagnosis are that the cysts evert when the pupil is dilated, are usually multiple, not only in the same eye but in the fellow eye, do not splint the iris in dilatation, and do not usually bulge the stroma of the iris forward, nor usually produce secondary changes in the overlying iris stroma.

b. Pupillary cysts

The ring sinus of Szily present in the embryo and fetal eye (fig. 25) may remain somewhat patent in the adult eye. This patent space, or sinus, in the adult eye may enlarge and produce a localized cyst (figs. 26 and 27). Browning and Swan¹⁶ reported one of these cysts which enlarged under observation to such an extent that it interfered with vision and had to be removed. A pupillary cyst may become detached and settle in the anterior chamber (fig. 16). Such free cysts of the pigment epithelium may come also from detached intraepithelial cysts at the base of the iris (fig. 15). A free cyst in the anterior chamber was observed by Browning and Swan as a result of the hyperplasia of the pigment epithelium around the pupil following the use of a strong miotic.

CONCLUSIONS

In this discussion I have tried to point out the versatility of the pigment epithelium and

in this regard I have cited its ability to proliferate readily and reproduce its kind, its migratory capacity, its seeding and growing at most any distant site, and its secretory function (cuticular product). The pigment epithelial layer of the eye was then discussed from the standpoint of hyperplasias, tumors, and cystic formations as they affect the retina, ciliary body, and iris.

Many of the features discussed here are well known and they have been mentioned for the sake of completeness. Among the less appreciated conditions included in this report are the following:

1. Benign and malignant tumors of the iris pigment epithelium (figs. 11, 18, 19, and 21).
2. Transitional tumors between pigment epithelium and smooth muscle (fig. 20).
3. Nature and characteristic of intraepithelial and pupillary cysts of the iris (figs. 15, 16, 22, 23, 24, 25, 26, and 27).
4. Iris freckles from migration and proliferation of the pigment epithelium (figs. 5, 6, and 7).
5. Seeding of the iris pigment epithelium on iris (figs. 8 and 10) and cornea (fig. 9).
6. Primary localized hyperplasia adjacent to the disc (fig. 3).
7. Congenital atavistic hyperplasia at the pupillary margin (fig. 10).
8. Iris melanoma (hyperplasia) from migration and localized proliferation of pigment epithelium along the anterior surface of the iris (fig. 6).

73 East 71st Street (21).

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UNILATERAL PAPILLEDEMA*

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Papilledema is usually bilateral, or soon becomes so during the course of continued ophthalmoscopic observation. Occasionally, it is unilateral and remains so. This often poses a diagnostic problem and it is the purpose of this communication to review the causes of this relatively rare situation.

Let us first define papilledema. According to Paton and Holmes,¹ it is a passive edema of the nervehead due to raised intracranial pressure without primary inflammatory changes and often without disturbance of function. In contrast, they defined optic neuritis as a swelling of the disc associated with inflammation and loss of function. Thus, there are two separate entities which may resemble each other ophthalmoscopically in the early stages, in that they both give rise to an edema of the nervehead. In some parts of the country, the terms are used interchangeably. The use of the term "papillitis" adds to the confusion. Most ophthalmologists use this latter term to refer to an inflammation of the disc itself, associated with intraocular disease. Generally speaking, the optic neuritis cases, due to inflammation, are apt to be unilateral; whereas, the true papilledema cases, due to raised intracranial pressure, are bilateral. However, exceptions may occur.

When we speak of unilateral papilledema we must be sure it really remains unilateral. It is well known that the swelling of the nervehead, from raised intracranial pressure, often appears first in the eye with the lower intraocular pressure.² Thus, a unilateral case may turn into a bilateral one within a few days. With these points in mind, let us consider true unilateral papilledema. Walsh³ divides it, logically, into two categories:

- a. Associated with ocular orbital pathology.
- b. Associated with intracranial pathology.

OCULAR AND ORBITAL PATHOLOGY

1. CONGENITAL ANOMALIES OF THE DISC

Pseudopapilledema or pseudoneuritis, so called, is neither a papilledema nor a neuritis but so resembles these conditions that mistakes in diagnosis are frequently made. This congenital anomaly is usually bilateral but occasionally it is unilateral. It consists of a heaping up of nerve fibers on the disc due, possibly, to their crowded passage through a small scleral canal. The eyeball is usually misshapen, showing a large degree of hypermetropia and astigmatism. There is no enlargement of the blindspot, no dilation of the veins, and no hemorrhages. Also, the picture does not change on repeated observation. Other congenital anomalies of the nervehead may simulate an edema—such as, epipapillary membranes, drusen, and myeli-

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nated nerve fibers. Unilateral myopia with posterior staphyloma may also be mistaken for papilledema.

2. UNEQUAL PRESSURE CHANGES IN THE TWO EYES

Sudden lowering of intraocular pressure gives rise to a slight but definite elevation of the nervehead. It may occur following any surgical procedure resulting in prolonged hypotension such as trephining, cyclodialysis, and so forth. It has been seen after cataract surgery when a wound leak persists or following perforating trauma to the eyeball with fistula formation. This is a true papilledema with no inflammatory element. Pre-existing glaucoma with elevated tension in one eye would favor the appearance of a papilledema in the eye with the lower tension in the event of the intracranial pressure being substantially increased.

3. INTRAOCULAR DISEASE

A posterior uveitis may produce a papillitis by direct extension of the inflammation of the nervehead. An example of this is Jensen's choroiditis juxtapapillaris which may be confused with an optic neuritis of the nerve trunk because of the blurring of the disc. The sector-shaped defect in the field differentiates it however. In certain cases of anterior uveitis a papillitis may occur by diffusion of toxic material through the vitreous to the nervehead.

4. OPTIC NERVE DISEASE

Acute infectious disease may attack one optic nerve only and give rise to a unilateral swelling of the disc associated with loss of function. Syphilis and tuberculosis have been known to produce this through involvement of the meningeal sheaths. Metastatic foci from infectious disease elsewhere may affect one optic nerve. The demyelinating diseases may or may not cause edema of the disc. In general, the nearer the lesion is to the disc, the more likely the chance of its producing congestion visible ophthalmoscopically.

Primary tumors of the nerve usually cause early atrophy without any papilledema. Occasionally, however, when the location is such as to obstruct venous return from the disc, a papilledema may occur. Also extension of the tumor itself down the nerve to the disc, with accompanying gliosis, may simulate a choked disc. Most optic-nerve tumors are, sooner or later, accompanied by some degree of exophthalmos, usually straight forward. Those occurring in early childhood are usually gliomas, whereas those seen in middle life are apt to be meningiomas.

5. VASCULAR DISEASE

An obstruction of the central retinal vein can produce enough vascular congestion to cause edema of the nervehead. (Branch obstructions do not.) The swelling of the disc is relatively slight. Many hemorrhages are present throughout the retina and signs of vascular disease are found in other retinal arteries and veins.

6. ORBITAL TUMORS

Orbital tumors, even large ones, usually show no sign of pressure on the optic nerve or any blockage of venous return flow from the disc. Occasionally, they do, however, and they must always be kept in mind in any case of unilateral papilledema, especially if any unilateral exophthalmos is present with displacement of the globe.

7. ORBITAL INFECTIONS

Orbital cellulitis or abscess rarely causes pressure on the optic nerve but may do so, resulting in some congestion at the disc. Also rare is the direct extension of purulent sinusitis to the nerve, producing a neuritis.

INTRACRANIAL PATHOLOGY

Although the great majority of cases of papilledema associated with increased intracranial pressure are bilateral, there are some which exhibit only unilateral involvement. In a study of 638 such cases Bregeat⁴ found that 8.5 percent remained unilateral.

1. BRAIN TUMORS

A meningioma of the sphenoidal ridge is characterized by a tremendous hyperostosis and often invades the orbit. Unilateral exophthalmos and atrophy of the optic nerve is the rule. Occasionally, however, one sees a unilateral papilledema in addition.

The classic example of unilateral papilledema associated with increased intracranial pressure is seen in the Gower-Paton-Kennedy syndrome commonly called the Foster-Kennedy syndrome.⁵ In this situation a brain tumor situated at the base of the frontal lobe near the entrance of the optic foramen presses on one optic nerve causing atrophy and shutting off its vaginal sheath thus preventing the transmission of the increased intracranial pressure to the disc. However, the opposite nervehead shows papilledema because of the generalized increased pressure within the cranial cavity. It is seen chiefly in the olfactory groove meningiomas which often give rise to anosmia in addition. Other tumors or vascular anomalies of the middle fossa may also produce this syndrome.

A somewhat similar mechanism is seen when inflammatory adhesions have formed around one nerve following a syphilitic meningitis resulting in partial atrophy. Later, if a generalized increase of intracranial pressure should occur from any cause, a unilateral papilledema would develop on the side opposite the one with adhesions.

2. BRAIN ABSCESS

This condition rarely causes papilledema but when it does, homolaterality is the rule, according to Uhthoff.⁶ It is difficult to explain why this is so. Perhaps the accompanying cerebral edema interferes with the great venous sinuses in some way, causing significant disturbances of circulation on one side.

3. VASCULAR ANOMALIES

There are several reports in the literature⁷ of unilateral papilledema associated with enlargement of the ophthalmic artery just as

it enters the optic canal. In these cases cranial exploration has shown the aneurysm pressing on the nerve. Why homolaterality occurs is hard to explain when the pressure is applied so far back.

Through the cavernous sinus almost all the venous blood of the eye and orbit is drained. Therefore any lesion in the sinus blocking this return flow may result in dilatation of all contributory veins including the retinal veins and even mild congestion of the nervehead on one side. An example of this is seen in arteriovenous aneurysm of the cavernous sinus which gives rise to a pulsating exophthalmos and sometimes unilateral papilledema.

Thrombosis of the cavernous sinus from infection may also cause a mild unilateral papilledema. This may change to a bilateral papilledema if the thrombosis spreads to the other side.

Before the venous blood reaches the cavernous sinus it passes through the ophthalmic vein which leaves the orbit via the superior orbital fissure. At this point interference with the return flow of blood might be enough to cause congestion of the disc.

In all these instances of blockage of venous return by lesions posterior to the orbit, there are usually enough anastomoses with the anterior facial vein and pterygoid plexus to prevent marked congestion at the disc. Therefore, when unilateral choked disc occurs in these conditions one must assume some abnormality of the collateral circulation, or else some peculiar development of the great sinuses which allows high venous pressure in one ophthalmic vein. This abnormality of the venous sinuses, particularly the transverse sinus, has been emphasized by Swift⁸ and by Woodhall⁹ and may account for some otherwise unexplained case of unilateral papilledema.

SUMMARY

1. Unilateral papilledema is usually associated with ocular or orbital pathology causing obstruction of venous return from the disc.

2. Intracranial pathology may also produce it on occasion. In this latter category are found tumors of the frontal lobe giving rise to contralateral papilledema through the Gower-Paton-Kennedy syndrome, and vascular anomalies acting by the same mechanism. Brain abscess, on the other hand, is apt to cause homolateral choking. Variations in the great venous sinuses giving rise to increased pressure in one ophthalmic vein may be responsible in certain cases.

3. Localized postinflammatory changes in the optic nerve sheaths on one side may result in the development of contralateral swelling of the disc should a subsequent rise of intracranial pressure occur.

4. Unequal intraocular pressure between the two eyes favors the development of a mild papilledema on the side with the lower pressure.

243 Charles Street (14).

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PROBLEM CASES IN NEURO-OPHTHALMOLOGIC DIAGNOSIS*

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Many patients with neurosurgical lesions present ocular symptoms and signs which require the cooperation of the ophthalmologist. The problem cases discussed in this paper have been studied in joint conference between the neurosurgeon and ophthalmologist, often on several occasions. Such an arrangement is mutually advantageous, and serves also as a useful teaching exercise for residents in both fields. A review of problem cases may sharpen our diagnostic faculties and point out errors which may be avoided in future patients.

Meningioma of the sphenoid wing presents such a mutual problem in diagnosis. These expanding lesions of the "sphenosellar recess" produce symptoms which often lead the patient to the ophthalmologist first: (1) visual loss, (2) exophthalmos, (3) disorders of ocular motility, and (4) orbital pain. The

meningiomas of the sphenoid ridge have been classified by Cushing and Eisenhardt¹ into three arbitrary groups according to the portion of the ridge involved. The first group is that of the inner or deep ridge nearest the sella, overlying the superior orbital fissure and the cavernous sinus. The second includes those tumors of the middle or alar portion involving the middle third of the ridge. The third group shows primary involvement of the outer or pterional portion adjacent to the lateral wall of the cranial vault and is more likely to consist of a meningioma en plaque.

While this classification is useful in localization, it soon becomes evident that individual cases do not necessarily fall into such clear-cut diagnostic categories. The following patients demonstrate this point.

CASE 1

A 33-year-old white married woman complained of prominence of the right eye present for one month. Ocular examination showed corrected vision

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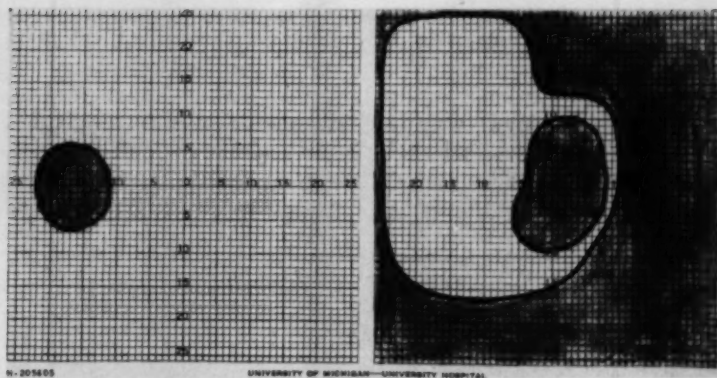


Fig. 1 (Henderson). Case 1. Tangent screen findings with six-mm. white, O.D., and two-mm. white, O.S., at one meter.

reduced to 20/30 in the right eye. Proptosis of 3.5 mm. was measured, with some downward displacement, and no resistance to retropulsion. The ocular motility was full, a four-diopter papilledema was present on the right only, and a definite decrease in myopia had occurred in the right eye. An enlarged right blindspot was the only field defect. All other studies, including X-ray films of the skull, optic foramina and sinuses, were normal. Because of the proptosis, choked disc, and evidence of pressure behind the globe, with associated reduction in myopia, a mass in the muscle cone was postulated and a Berke-Krönlein orbitotomy performed. No orbital lesion was found. During the postoperative course the myopia gradually reappeared and the papilledema regressed.

A year later the patient returned with sudden visual loss in the right eye. She was four and one-half months pregnant. The right vision was now only "moving objects" as compared to corrected

20/20 acuity in the left eye. Early pallor of the right disc, early choking of the left disc, and 3.5 mm. proptosis of the right eye was present. On visual field examination (fig. 1) right optic nerve involvement was coupled with left blindspot enlargement.

X-ray examination now showed increased density of the right sphenoid ridge, compatible with sphenoid-ridge meningioma. In review of the previous films the abnormality was minimally present but not as well defined. After arteriography confirmed the lesion, a craniotomy was performed with subtotal excision of an extensive sphenoidal-ridge meningioma en plaque on the right. Both optic nerves and the chiasm were involved, and thorough decompression of these structures was carried out.

Postoperatively no visual improvement occurred; although papilledema regressed completely on the left, optic atrophy increased on the right. The right visual field showed an inferior defect (fig. 2). Since

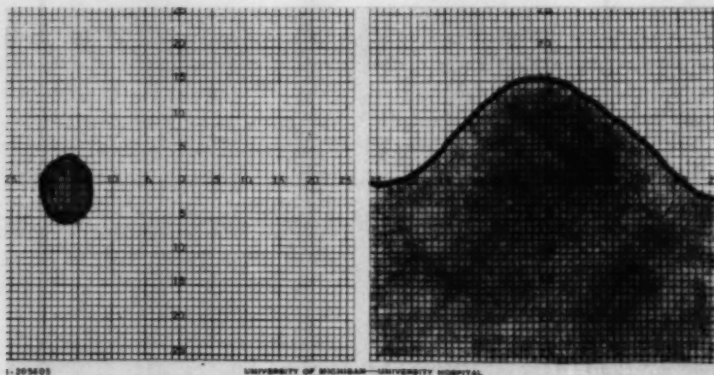


Fig. 2 (Henderson). Case 1, postoperative. Tangent screen findings with 36-mm. white, O.D., and two-mm. white, O.S., at one meter.

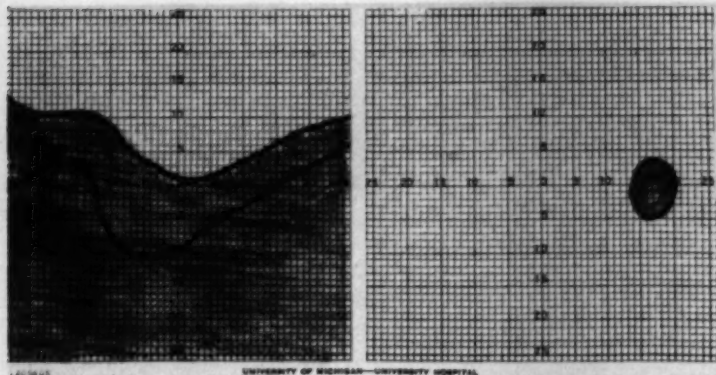


Fig. 3 (Henderson). Case 2, postoperative. Tangent screen findings with two-mm. white, O.D., six-mm. white and 18-mm. white, O.S., at one meter.

that time, there has been evidence of slow tumor growth in the right orbit although no further sign of visual involvement has occurred in the left eye. Future right orbital decompression may be necessary.

CASE 2

A 42-year-old white married woman had noted ptosis of her left upper lid increasing gradually over a five-year period. For two years there had been diplopia in the extremes of gaze. Occasional severe occipital and left-sided headaches had been associated with a "film" over the left vision. Mild aching in the left orbit had been present on occasion. A marked change in refractive error of the left eye with a shift toward hyperopia had occurred, and two weeks before the referring physician had found a minimal left proptosis.

Examination showed visual acuity reduced to 20/70 in the left eye. There was lag of movement of the left eye in all diagnostic positions together with mild ptosis and 2.5 mm. of left proptosis. The discs were normal and no visual field defect was found. X-ray films showed sclerosis of the lesser and greater wings of the left sphenoid, also involving the left optic foramen and orbit.

At craniotomy, marked hyperostosis due to meningioma en plaque was found at the inner end of the left sphenoid ridge, extending laterally. The hyperostotic bone was loose and gradually removed. The tumor completely surrounded the left optic nerve intracranially and entered the optic foramen which was also hyperostotic. The nerve was therefore decompressed.

Postoperatively, the vision in the left eye was reduced to finger counting. No change in motility was noted except for a mild pseudo-von Graefe reaction of the left upper lid. The left optic disc showed early temporal atrophy and the right eye was normal. The visual field demonstrated a dense inferior altitudinal defect (fig. 3).

CASE 3

A 29-year-old white married woman noted shortly after delivery of her first child two years ago a drooping of her left upper lid persisting for six weeks. Minimal blurring of vision gradually developed into diplopia in the extremes of gaze. Ocular examination at that time showed a slight difference in visual acuity together with 2.5 mm. of ptosis of the left upper lid and red-glass diplopia to the right. On Neostigmine injection the diplopia disappeared but no effect on the ptosis resulted. A diagnosis of mild myasthenia gravis was entertained by the neurology consultant, but the symptoms and findings improved spontaneously.

Recently the ptosis has returned and left supra-orbital headaches have been complained of and, because of increasing diplopia and prominence of the left eye, further studies were initiated. There is still only minimal visual reduction on the left. An incomplete external and internal left oculomotor palsy is present with 1.5 mm. of left proptosis and early visible congestion of the left optic nervehead. Neurologic examination is normal and the spinal fluid negative. X-ray films of the skull show a localized overgrowth of bone in the left parasellar region involving the lesser wing of the sphenoid, and a small meningioma en plaque must be considered as most likely.

Because of the experience with the two previous cases surgery has been delayed, and repeated follow-up examinations have shown no progression of findings over the period of a year. The internal ophthalmoplegia has recovered.

These cases have certain factors in common. The relatively prolonged history of slow growth is characteristic. The relationship to pregnancy in two is of interest, and the fluctuation of findings in these patients

indicates an endocrine relationship. Kearns and Wagener² have summarized this point stating that the predilection for occurrence in women seems to indicate a hormonal influence in the growth of meningiomas. This appears to be especially true in pterional tumors en plaque, since all such instances in Cushing and Eisenhardt's series occurred in females. Histologic evidence has also been reported that the cytoplasm of the tumor cells becomes more swollen during pregnancy.

Of interest also is the fact that none of the patients showed the fullness in the temporal region supposedly characteristic of meningioma en plaque. In all three the lesion gave indication of primary involvement of structures at the inner region of the sphenoid ridge and the orbital apex rather than the pterional portion adjacent to the lateral wall of the cranial vault.

The indications for surgical interference in these tumors are subject to dispute. Smith³ has recently stated that the primary reasons for operation in a sphenosellar lesion are (1) uncontrollable pain, (2) a progressive threat to vision in *both* eyes, and (3) increased intracranial pressure. Certainly one might agree to delay in the surgical treatment of these lesions in terms of their slow growth, but should one delay until involvement of *both* optic nerves is present? Since direct involvement of one optic nerve means that the tumor has already involved the inner end of the sphenoidal ridge, should not the advancing tumor be removed as completely as possible at this time before its advance has implicated the chiasm as well as the other optic nerve? If the evidence of optic nerve damage as a direct result of surgery in the first two cases is any indication, earlier surgery, might well be advantageous.

The shift in refractive error toward hyperopia in the first two patients is also of interest. This certainly occurred without the presence of tumor within the orbit in the first case, since none was found on orbital exploration. There most probably is a rela-

tionship to vascular congestion at the orbital apex.

The typical picture of a Foster-Kennedy syndrome in the first patient was present at the time the true diagnosis was first determined. Such a change in the optic nerves is much more frequent in sphenoid wing meningiomas than in the olfactory groove meningiomas originally associated with the syndrome. For example, Bynke⁴ has reported 17 instances of Foster-Kennedy syndrome in 1,400 cases of expanding intracranial lesions, and 11 of the 17 were found due to sphenoid-wing meningioma. Only two patients had meningiomas of the olfactory groove. It is likely that the papilledema in the second eye in sphenoid-wing meningioma is due to local involvement of the optic nerve and orbital apex rather than to the increased intracranial pressure usually considered causative. The higher incidence of Foster-Kennedy syndrome in these cases is also noted by Kearns and Wagener² who suggest that the presence of papilledema in one eye and optic atrophy in the other should suggest the diagnosis of sphenoid wing meningioma if the sense of smell is normal.

The diagnosis of retrobulbar neuritis may appear unequivocal in many patients, especially if improvement occurs on administration of corticosteroids or other treatment, but it should be emphasized that in certain cases the true diagnosis of intracranial disease may be masked. Therefore *the responsibility for the diagnosis of retrobulbar neuritis is a continuing one*. The following problem cases will reinforce this statement.

CASE 4

A 35-year-old married white woman complained of sudden visual loss in the right eye present for several weeks. The visual acuity was reduced to 20/200 on the right with normal motility, normal nerve heads, and a large right centrocecal scotoma present on field examination. Retrobulbar neuritis was diagnosed and treatment first of Meticorten, then vasodilators was followed by gradual improvement to 20/20 over the period of a year, with a tiny residual central scotoma. At that time the right vision suddenly became worse, and a hemianopic field contracture occurred (fig. 4).

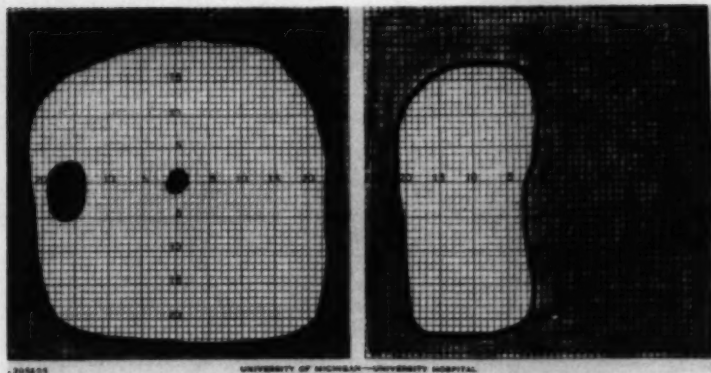


Fig. 4 (Henderson). *Case 4*. Tangent screen findings for two-mm. white at one meter. Left central scotoma to two-mm. red at one meter.

Skull X-rays and a normal spinal fluid examination were accompanied by a negative neurologic survey except for early right optic atrophy. Six weeks later she was admitted as an emergency because of sudden profound visual loss in the left eye. Beginning improvement on vasodilator therapy occurred, and bilateral carotid arteriograms were interpreted as normal from the wet films. On discharge from the hospital vision was moving objects, O.D., and 20/70+, O.S. with a centrocecal field defect on the left, suggesting a possible vertical cut (fig. 5).

On her next return visit the previously overlooked final X-ray report on the arteriography was discovered, suggesting the presence of a space-occupying lesion anterior to the sella turcica in or close to the midline. On craniotomy a large meningioma of the tuberculum sella was removed. The tumor was seen to extend suprasellarly to compress the optic chiasm and both optic nerves. Postopera-

tively right vision failed to bare light perception, and left vision returned to 20/20. Right primary optic atrophy was accompanied by minimal left field contracture.

This patient points out the delay in appearance of the usual diagnostic criteria presented for suprasellar meningiomas. The characteristic Cushing's triad of primary optic atrophy, bitemporal field defects, and a normal sella turcica is said to be diagnostic. However, Fanta⁵ has reported on a series of 22 such cases, and only a few of these satisfied the criteria of Cushing's triad. Only two patients presented bitemporal hemianopia, while all the rest demonstrated an asymmetrical development of visual field loss, most

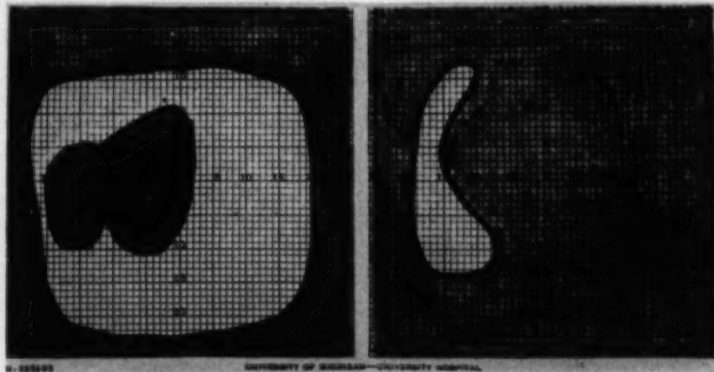


Fig. 5 (Henderson). *Case 4*. Tangent screen findings for 40-mm. white, O.D.; one-mm. white and two-mm. white, O.S., at one meter.

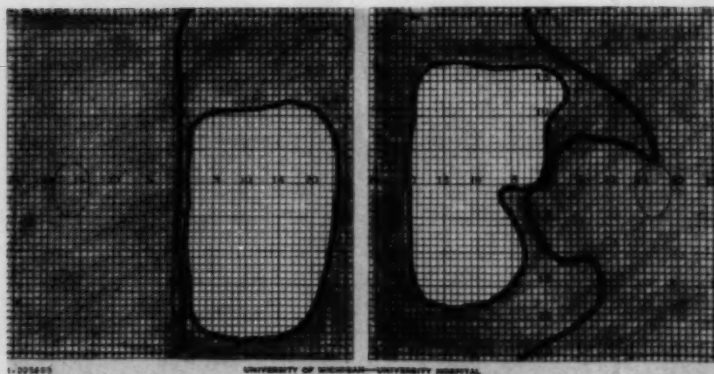


Fig. 6 (Henderson). Case 5. Tangent screen findings for two-mm. white and nine-mm. white at one meter.

often beginning unilaterally. All his cases, however, showed unilateral or bilateral optic atrophy. The patient just described presented an early monocular visual loss and a suggestion of vertical field cut, pointing to chiasmal disease. Response to steroid and vasodilator administration concealed the true diagnosis.

CASE 5

A 34-year-old Hawaiian physician suffered sudden loss of vision in his left eye 18 months ago. Visual acuity was reduced to 20/100 on the left, there was no specific field defect reported, and skull films were normal. Optic neuritis was diagnosed and vision returned to 20/30 after a month of treatment. Nine months later visual blurring recurred in the left eye, with acuity down to 20/80 and a left temporal field cut present. Visual loss was then progres-

sive, with gradual appearance of a pronounced bitemporal hemianopia. Skull films were repeated and now showed an enlarged sella turcica.

The first ocular examination at University Hospital demonstrated acuity of 20/60, O.D., and counting fingers, O.S., with primary optic atrophy on the left and an irregular bitemporal defect on visual field testing (fig. 6). Craniotomy exposed a large pituitary adenoma stretching both optic nerves and presenting mostly anterior to the chiasm. Subtotal removal was followed by radiation therapy. A month later the vision had improved to 20/25, O.D., the atrophy remained O.S., and the visual field had improved (fig. 7).

This patient demonstrates original response to treatment despite the presence of an early pituitary adenoma, and points out the importance of repetition of studies in such cases, since the X-ray films showed a definite change.

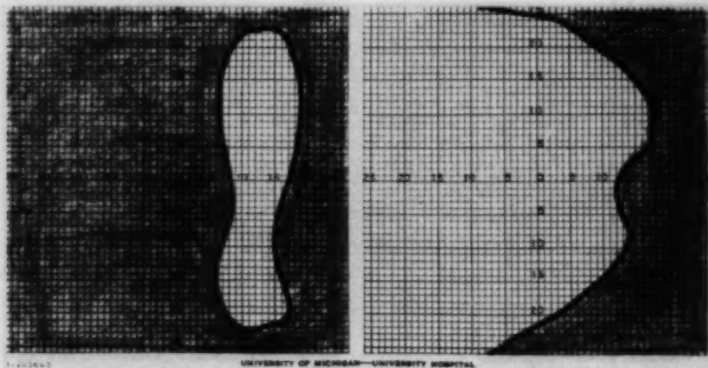


Fig. 7 (Henderson). Case 5. Tangent screen findings for two-mm. white at one meter.

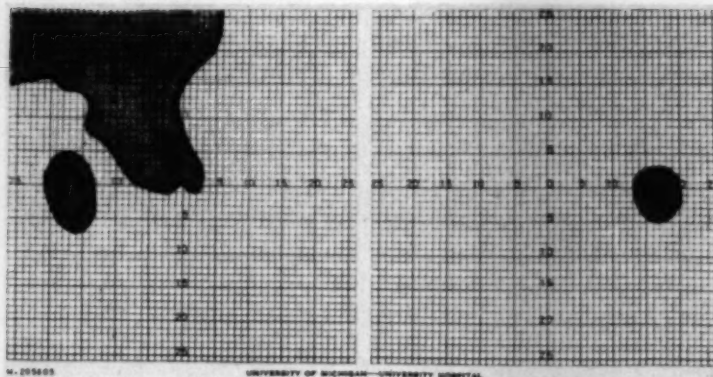


Fig. 8 (Henderson). Case 6. Tangent screen findings for two-mm. white at one meter.

CASE 6

A 19-year-old youth, a college student, complained of blurred vision in the left eye with associated severe headaches involving the left side of the face. Visual acuity was: 20/15, O.D.; 20/20, O.S. The visual field showed an atypical central scotoma (fig. 8). No other positive findings were noted on extensive diagnostic studies except for a spinal fluid protein level of 45 mg. percent (normal 15 to 40 mg. percent). A diagnosis of acute retrobulbar neuritis was made and treatment with steroids initiated. Vision fluctuated but gradually improved to 20/25 in the left eye after first falling to 20/50, and a variable visual field defect showed its greatest improvement four months after the onset (fig. 9).

The treatment was gradually tapered and stopped but the visual defect fluctuated until admission to the hospital five months later because of severe continuing left frontal headaches and retro-orbital pain. At this time early optic atrophy was visible on the left, with left visual acuity of 20/50, and the skull films now showed parasellar erosion, more marked

on the left. The spinal fluid showed a protein level of 61 mg. percent. Arteriography confirmed the tumor and, at craniotomy, a large extrasellar chromophobe adenoma was seen between the left optic nerve and left internal carotid stretching the nerve and pushing it medially. Subtotal removal was followed by radiation therapy. In retrospect, mild pituitary signs had been present, such as decreased need for shaving and a moderate weight gain.

This patient again shows original response to treatment, and the importance of repeated studies is evident. In addition the pain was definitely not typical of a retrobulbar neuritis.

CASE 7

A 30-year-old white man, an industrial worker, was seen with a complaint of blurring of the left vision with intermittent aching in the left orbit. Vision was: 20/15, O.D., 20/25, O.S., with a tiny

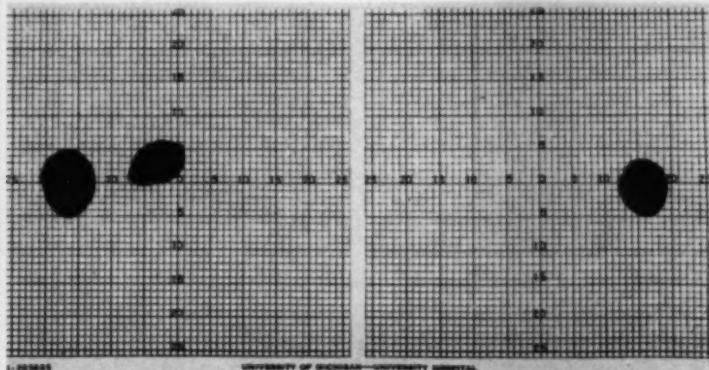


Fig. 9 (Henderson). Case 6. Tangent screen findings for two-mm. white at one meter.

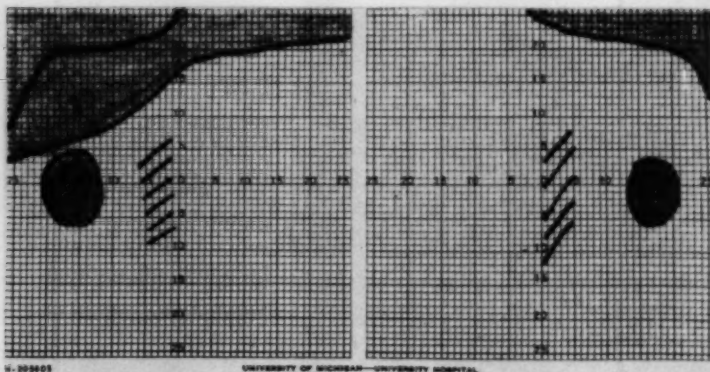


Fig. 10 (Henderson). *Case 7*. Tangent screen findings for one and two-mm. white, O.S., for one-mm. white, O.D. all at one meter. The dark hatching represents relative loss to two-mm. red at one meter.

central scotoma on the left. The referring physician's diagnosis of retrobulbar neuritis was confirmed and the patient returned to him for a period of corticosteroid treatment. He returned two months later with no improvement and no change in the ocular examination.

At this time a neurologic examination was normal and skull X-ray films showed an enlarged sella turcica with intrasellar erosion. After a normal arteriogram it was elected to follow the patient. The visual field showed minimal progressive changes for two months and at that time early bitemporal findings were noted (fig. 10). The visual acuity was unchanged, the left pupil showed a slower direct light reaction, and he still complained of intermittent aching in the left orbit. Pneumoencephalography was normal, although extension of the mass into the sphenoid was noted. Spinal fluid protein at this time was 50 mg. percent. Radiation therapy was elected and recovery has followed.

This patient points out the delay possible in reaching the proper diagnosis when the original diagnostic examination is not complete, and further emphasizes the need for persistence in examination when a retrobulbar neuritis appears atypical.

CASE 8

A 30-year-old white woman gave a past history of decreased vision, O.D., four years ago. This was diagnosed as retrobulbar neuritis, was treated with typhoid injections and ACTH, and improved slowly over a period of months of such therapy. Associated amenorrhea, hirsutism, and hyperpigmentation of the skin gradually increased, and abdominal exploration was performed because of the presence of Cushing's syndrome but normal adrenals were found. Progressive findings of Cushing's syndrome

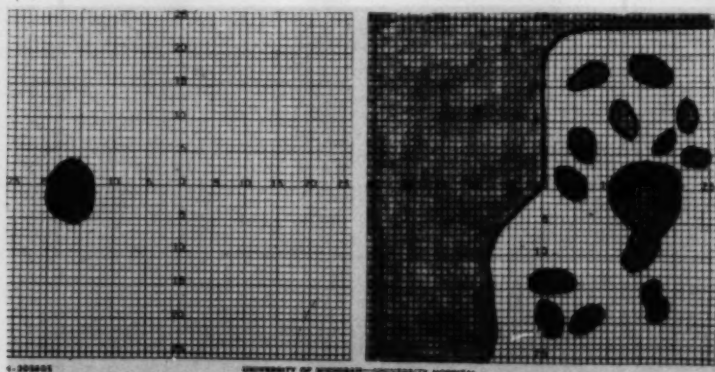


Fig. 11 (Henderson). *Case 8*. Tangent screen findings for two-mm. white at one meter.

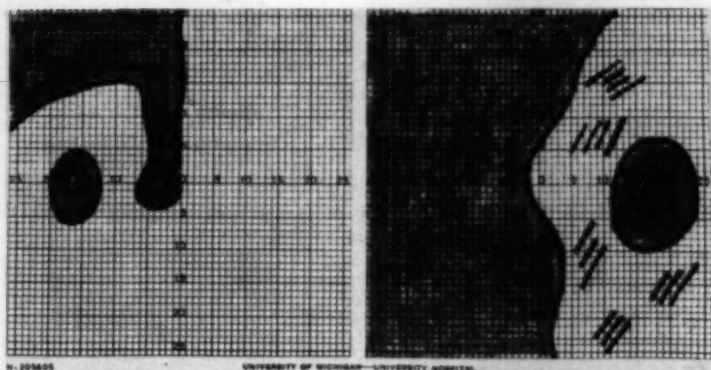


Fig. 12 (Henderson). *Case 8*. Tangent screen findings for two-mm. white at one meter.

with elevated ketosteroid levels led the following year to complete right adrenalectomy and subtotal left adrenalectomy. Maintenance level steroids were continued and a year ago amenorrhea and hyperpigmentation recurred.

When a gradual visual decrease appeared in the right eye, similar to the episodes four years previously, she was seen in our department. The vision was: 20/40, O.D., and 20/20, O.S., with normal fundi. The visual field demonstrated an atypical defect (fig. 11). The possibility of recurrent retrobulbar neuritis was raised and steroid administration was increased. Within two weeks the vision decreased to 20/200, O.D., and 20/30, O.S., with a further vertical midline defect also present in the left eye (fig. 12).

At this time an organic chiasmal lesion seemed definite and neurosurgical consultation showed a slightly enlarged sella on X-ray films, with arteriographic findings of a suprasellar mass, more on the right. The spinal fluid protein was 49 mg. percent with a 2+ globulin.

At craniotomy a large chromophobe pituitary adenoma was subtotally removed. It was subchiasmal in location and extrasellar beneath the right optic nerve. With postoperative radiation therapy, vision has improved to 20/50, O.D., and 20/20, O.S., and the visual field shows regression of the defect (fig. 13).

This patient points out the importance of a vertical midline type of visual field cut in pointing to chiasmal involvement. This was not appreciated until both eyes showed such a change.

There has been recent interest in the occurrence of pituitary tumors in patients with Cushing's syndrome. Kearns and his associates⁶ found that 12 of a series of 122 patients with adrenal hyperplasia and Cushing's syndrome had either clinical or histologic evi-

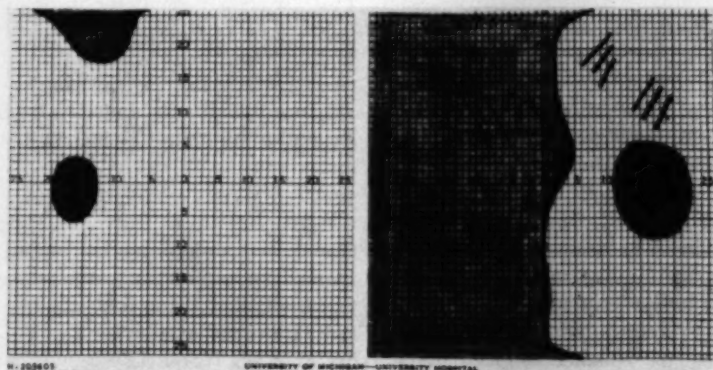


Fig. 13 (Henderson). *Case 8*, postoperative. Tangent screen findings for two-mm. white at one meter.

dence of pituitary tumor. The ocular findings were chiasmal field defects in five of the 12 and paralysis of the oculomotor nerve occurred in four. Six of the 12 cases had no ocular abnormalities. The incongruity of the field defects with associated oculomotor involvement pointed to extrasellar extension of the chromophobe adenomas found in all six of these patients. Salassa and others⁷ feel that adrenal resection may actually have stimulated the growth of these pituitary tumors, and other authors^{8,9} voice the same opinion. It is emphasized that X-ray films of the pituitary fossa should be taken at regular intervals after adrenalectomy for Cushing's syndrome.

The view of our endocrinologist is that the original administration of ACTH over a prolonged period may have produced an iatrogenic Cushing's syndrome. However, whether a chromophobe adenoma was present in minimal size prior to the entire episode cannot be determined.

It will be noted that in three of the four patients with pituitary adenoma just presented there was an elevation of the spinal fluid protein, usually of low degree. All three patients showed evidence of extrasellar extension of their lesion. Bakay¹⁰ has shown the importance of such a finding in a series of 50 patients with tumors of the sellar region. The cerebrospinal fluid protein level was normal in those pituitary adenomas which were confined to the sella turcica, with no tumor tissue breaking through the diaphragma sella, but 90 percent of the adenomas with extrasellar extension demonstrated an increased protein. This further emphasizes the importance of an early lumbar puncture in problem cases with atypical optic nerve involvement.

It should be noted from these patients that improvement of vision and of the visual field defect in response to steroid therapy may mask the underlying pathology. We must recall that such treatment is capable of alleviating the conduction block in the

visual pathway by its nonspecific anti-inflammatory action without having any lasting effect on the primary disease. Consequently, one should learn to view any case of unilateral visual loss with a long-range type of suspicion, and must be prepared to repeat the basic studies especially in the case of recurrence of findings. The important clue in several of the cases was in retrospect the atypical pain present in the orbital region, and its persistence even with demonstrable improvement in vision and in the visual fields.

All of the cases presented in this paper fall within the age group where the most likely cause of retrobulbar neuritis is multiple sclerosis. Such patients should not be dismissed from continued observation, even with original improvement on treatment, since the true diagnosis may be reached by persistence, especially when recurrence ensues or when the associated findings are atypical.

SUMMARY

A group of interesting problem cases in neuro-ophthalmologic diagnosis has been presented. It is noted that fluctuation in symptoms and signs in meningioma en plaque appears to bear a relationship to endocrine changes in women. The criteria for surgical treatment are discussed in terms of visual involvement, and the occurrence of the Foster-Kennedy syndrome in this disease is noted. The responsibility for the diagnosis of retrobulbar neuritis is shown to be a continuing one, since original response to therapy may mask the underlying pathology. Repetition of studies is indicated whenever improvement fails to occur over a period of observation, and certainly at such time as recurrence with any atypical features appears. The possible importance of an elevated spinal fluid protein as a clue to extrasellar extension of a chromophobe pituitary adenoma is pointed out.

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HELMHOLTZ THE MUSICIAN

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Francis Adler the ophthalmologist, teacher, physiologist, writer, and editor is widely known. Less well known is Francis Adler the accomplished and cultivated musician. A Festschrift dedicated to so versatile a man would be incomplete without reference to this facet of his attainments. That is the reason for writing a note on one of his distinguished predecessors in science and culture.

Hermann von Helmholtz was perhaps the greatest musicologist who ever lived. He was familiar with the univocal music of antiquity,* the multivocal music of the middle ages, and the harmonic music of his own time. He knew what there was to be known of harmonic constituents, octaves of the prime, majors, minors, fundamentals and overtones. When he was a young military surgeon he heard quite literally and with no thought of poetry, "melodies and chords" in the plashings of the fountain jets at Sans Souci; and

later had no difficulty in hearing the overtones and detecting the partials in the human voice. Was he also a musician? Marmelszadt,¹ Thorek,² and Garrison³ referred to him as such, and so, with more but still insufficient evidence, did McKendrick.⁴

How can we discover if music appealed to Helmholtz emotionally as well as intellectually? It would be too much to expect that the formidable *Lehre von den Tonempfindungen als Physiologische Grundlage für die Theorie der Musik* would yield much information on that point. A mathematical physicist would hardly write of his own feelings in a classic Principium. In fact, Helmholtz shied away from what he called "the complexity of psychological motives that here come into play." He was, he said, "merely a dilettante in such matters." He did to be sure discuss the esthetics of music, but no more than enough to indicate his essential agreement with Kant that the beautiful satisfies through its harmony of form with knowledge. "Beauty," he wrote, "is subject to laws and rules depending upon the nature of human intelligence,"

* Helmholtz wrote to Lady Kelvin that he had found many of the ancient forms of music preserved in the Scottish ballads.

and again, "The phenomena of purely sensual harmony are indeed only the lowest grade of musical beauty. Consonance and dissonance are but the means, albeit an essential and powerful means, to the higher and more spiritual beauties of music."

From this it is obvious that we must look beyond his publications for any information on Helmholtz's own emotions. Nevertheless, it is from the effect of his writings on one of his colleagues that we obtain a hint of where to turn for light on our problem. Helmholtz had stated "Among our great composers Mozart and Beethoven are only at the beginning of the period in which equal temperament predominated. Mozart still had opportunities of making extensive studies in the composition of songs. He is a master of the sweetest melody whenever he desires it, but in this he is almost the last. Beethoven's bold genius took possession of the domain which the development of instrumental music brought him. In his hands it was the pliant and appropriate tool which he was able to manipulate as none else had ever done. But he always treated the human voice as a handmaid, and consequently it never lavished the highest magic of its melody upon him."

This view aroused considerable annoyance in his friend Karl Ludwig, then professor of physiology at Leipzig. Helmholtz thereupon wrote to him as follows:

"In your last letter from Leipzig you attack my remarks on Beethoven. Perhaps I had better not have expressed myself merely critically about him if I did not wish to be misunderstood, for I too find in him the mightiest and most moving of all composers. I myself play hardly anything but Beethoven when I do play. Had I been speaking about the vehicle of musical emotion I should certainly have placed him above all others. I was, however, talking exclusively of melody and the fine artistic beauty of the flow of harmony, and there I do hold Mozart to be the first even if he does not affect us so powerfully. Speaking generally, as one grows older and bears more scars within one's

breast, one ceases to feel that emotion is really the greatest thing in art."

This revealing contrast between the textbook and the letter in discussing the same subject directs us to a study of Helmholtz's correspondence. Fortunately, most of this is available in the monumental biography by Königsberger,⁵ his friend and colleague at Heidelberg.

The first relevant letter was written to his father shortly after Helmholtz, then 17 years of age, began his studies at the Royal Friedrich-Wilhelm Institute in October, 1838. He wrote that he had encountered difficulties with some of the authorities over his piano. There was no room for the instrument in his quarters but he finally was allowed to install it next door. In reply his father warned him not to let his "taste for the solid inspiration of German and classical music be vitiated by the sparkle and dash of the new Italian extravagances—these are only a distraction, the others are an education." Responding, Helmholtz wrote: "Other people's expressions and execution seldom satisfy me: I always care much more for music when I am playing it myself." Later he wrote: "Any spare time I have during the day is devoted to music; and so far even on the worst days I have put in about an hour, and more on Friday, Saturday, and Sunday. By myself I play sonatas of Mozart and Beethoven, and with my chum* the new things he gets hold of which we run through at sight."

In 1847, Helmholtz met Olga von Velten whom he married shortly afterward. On one occasion during his betrothal he expected her to attend a concert with him but she failed to appear. He wrote to her that because she was not there, "my ear had heard only musical figures, my soul nothing." He might just as well, he went on, have been "listening to scales on the piano." By the end of the concert he had apparently recovered

* This was his first room-mate, who played the piano. The second played the flute "with no idea of time."

somewhat judging by his comments on the *Coriolanus Overture*: "A jewel—so short, so convincing, so decided and proud amid a host of restless and entangled motifs; while it dies off so sadly in melancholy strains—an unsurpassable masterpiece."

Olga had a good voice—"more practiced than mine"* he wrote to Donders—and it was she who sang into the piano, setting the strings in vibration and furthering her husband's study of vowel tones.

About this time Helmholtz wrote to his father that he had traveled to Coblenz in order to hear a concert of Beethoven's works; and shortly afterward he wrote from Munich—"Oedipus Colonus at the theatre, with Mendelssohn's music, but it is less inspired than his *Antigone*."

In 1863 while visiting Donders in Utrecht Helmholtz attended a "smoking concert." These affairs were really rehearsals for the great orchestral performances. In commenting on the program he described Liszt's *Symphonic Preludes* as "effective and extraordinary but hardly beautiful." He enjoyed the *Oberon Overture*, and considered Mendelssohn's *Variations Sérieuses* so fine that he suggested to his wife that she study them.

In 1865, Helmholtz attended a concert at the Conservatoire in Paris. He heard a symphony by Haydn, part of *Prometheus*, all of the *Midsummer Night's Dream*, a chorus of Bach, and Handel's *Hallelujah Chorus*. He wrote to his wife "One hears better choral singing in Germany, but the perfection of the orchestra is unique of its kind. The oboes in Haydn's symphony sounded like a gentle zephyr: everything was in perfect tune, including the high opening chords of the Mendelssohn overture, which are repeated at the end and usually sound out of tune. The *Prometheus* was the most enchanting melody, with the horns predominating. This concert, after the Venus of Milo, was the second thing

of purest beauty that life can give. . . ."

In 1875, he wrote: "Beethoven's op 130, which is inconceivably great and solemn but intensely sad, was clear for the first time to me today. The adagio was incomparably well played; it is a wailing of lost ideals, perhaps the prototype of Tristan's *Liebstd*, a formless surging of infinite melody."

A year later he wrote of Wagner that he and Frau Helmholtz ranged themselves "among the number of the master's inspired friends, and welcomed the new intellectual and emotional relations which, helpful and satisfying, became on both sides one of life's most cherished possessions."

It is now clear that Helmholtz had more than an intellectual appreciation of music, although the peculiar dichotomy of the musician-musicologist occasionally appears. For example, following an organ recital in Freiberg he wrote: "The organ is truly wonderful from the point of view of acoustics even more than from that of music," and commented on "the effects that could be produced . . . in regard to mass and power as well as to variety of timbre."

By his own account he was "not a good performer on any instrument although he knew something of all." For his personal use he preferred the piano, particularly the fine instrument given to him by Steinway of New York. It was on this piano that he played Bach's fugues in the middle of the night to "calm his intellect" when he could not sleep. His son, Richard, has left an account of having been instructed by his father in "the elements of thorough-bass." He does not, however, mention the effect of Bach on insomnia in the rest of the household.

Helmholtz died in 1894. Schumann's *Abendslied* which he had "often heard with emotion" was played at his funeral.

* Casey Wood, who knew Helmholtz and who on at least one occasion attended a highly informal *Bier-Microscopische Versammlung* in his company stated that the professor was "no mean vocalist."

* Helmholtz often used one form of art to make a point about another. When he first saw Titian's *Assumption of the Virgin* which he had known previously only from engravings, he wrote "Engravings are a worse substitute for this than a piano score for a symphony, since the beauty of the work consists of its miraculous light and color."

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THE TREATMENT OF CORNEAL DYSTROPHIES BY KERATOPLASTY*

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The large variety and relative infrequency of corneal degenerations and dystrophies often make their clinical identification difficult, and until a few years ago their treatment was largely palliative. It is the purpose of this communication to present: (1) a rather complete check list of these conditions, both a classification according to which corneal layer is primarily involved to aid in diagnosis, and a second classification according to etiology; (2) a brief description of the surgical technique used at present; (3) selected cases to illustrate the results obtained and some of the complications encountered; and (4) a discussion of the factors related to poor healing, the homograft reaction, and vascularization, with presentation of related statistics in a survey of 115 operations on cases of corneal dystrophy compared to 125 operations on other types of corneal opacification.

CLASSIFICATION

The term, "degeneration" implies the conversion of elements of acquired tissue into some inert substance; for example, changes after inflammation, known systemic disturbance or aging process. This usually begins in the periphery of the cornea at a later age. "Dystrophy" is a developmental and fre-

quently hereditary change in the original host tissue, which usually begins in the central cornea earlier in life. These two terms, degeneration and dystrophy, are used loosely because there is often much difficulty in making an etiologic diagnosis clinically, and a dystrophy may develop degenerative changes.

Clues to the correct diagnosis can often be obtained by noting from slitlamp examination which of the five corneal layers is primarily involved (table 1). On the other hand, it can be helpful to keep in mind possible etiologic factors, both local and systemic (table 2). Certain of the degenerations and dystrophies have no known cause, others are apparently related to aging processes, while others are predominantly hereditary.

SURGICAL TECHNIQUE

These operations have been performed during the past 10 years, the majority during the past few years at the Presbyterian-St. Luke's Hospital, the Illinois Eye and Ear Infirmary, and the Research and Educational Hospitals. Almost all have been performed by me, Howard L. Wilder, Lawrence H. Lassiter, or by the chief resident assisted by one of these three individuals.

Briefly, the present surgical technique is:

The operation is performed under local anesthesia, using a van Lint type of akinesia and 1.5 cc. retrobulbar injection of two-percent Xylocaine with epinephrine and

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hyaluronidase. The pupil has been previously constricted by several instillations of pilocarpine. A lateral canthotomy is performed. Superior and inferior recti traction sutures are placed.

Practically all of the operations reported here have been penetrating trephinations with direct suturing. The trephine is selected which will eliminate as much corneal pathology as possible, six or seven mm. being used most frequently. Because of the increased likelihood of anterior synechias forming, grafts of eight mm. or larger are used only when necessary to eliminate extreme areas of thinning or advanced pathology of the peripheral host cornea. When the edge of such a large or eccentrically placed graft is less than two mm. from the limbus, either a full iridectomy or multiple peripheral iridectomies or iridotomies are performed.

Using the Castroviejo tripod marker and methylene blue, marks are made on the host cornea outside of the anticipated trephination and on the donor cornea inside the subsequent trephination. Trephination is then performed on the donor cornea as completely as possible with the Guyton-Maumenee or the Castroviejo trephine and this is completed with the Katzin curved scissors for smaller grafts and the Castroviejo scissors for larger grafts.

Sutures of 8-0 black silk tied on Riedel needles are then passed through the marks on the donor cornea, approximately one-half way through the thickness of the cornea and about one-plus mm. long. In a few cases, 6-0 chromic catgut or 8-0 nylon has been used. A similar trephination completed with scissors is performed on the host cornea. The graft is immediately sutured and tied into position, using the three previously placed sutures. Wilder has recently introduced the use of a running suture in our hospitals. Each of these three sutures is then continued as a running suture to the region where the next suture is tied. The donor-host bite is made perpendicular to the incision. The run-

TABLE 1
CORNEAL DEGENERATIONS AND DYSTROPHIES
(ANATOMIC AND CLINICAL CLASSIFICATION)

EPITHELIUM

Hudson-Staehli line
Keratoconjunctivitis sicca
Neurotrophic keratitis
Associated with systemic conditions: Pityriasis, Sieman's disease, epidermolysis, chloroquin Rx.
Xerosis and keratomalacia
Epithelial dystrophy
Hereditary pitted (Reis)
Hereditary recurrent erosions

BOWMAN'S MEMBRANE

Pterygium
Band-shaped keratopathy (primary, or secondary to: ocular disease, uveitis in children, hypercalcemia, Fanconi's disease, Rothmund's disease, and ichthyosis)
Keratoconus
White ring of Coats
White limbus girdle of Vogt
Xanthoma cells and dystrophy (Dermo-, Chondro-, corneal D.)
Anterior-crocodile shagreen

STROMA

Arcus senilis
Cornea farinata
Keratoconus (anterior & posterior), keratoglobus, megalocornea
Marginal degeneration and Mooren's ulcer
Salzmann's nodular degeneration
Hereditary dystrophies (Groenouw's, etc.): granular, lattice, macular, congenital
Lipoidal dystrophy
Hurler's gargoylium
Crystalline deposits: systemic cystinosis, multiple myeloma, hereditary dystrophy

DESCMET'S MEMBRANE AND ENDOTHELIUM

Pigmentations: Krukenberg's spindle, Kayser-Fleischer ring, siderosis, chalcosis, argyrosis
Hassall-Henle warts (peripherally), cornea guttata (centrally), Fuchs' endothelial-epithelial dystrophy, bullous keratopathy
Glass membrane
Posterior embryotoxin
Posterior crocodile shagreen
Hereditary deep dystrophy

ning suture is adjusted to provide tight closure and slight outward puckering of the wound lips without creation of traction lines across the graft. The end of each running suture is then tied to the loose end of one of the initially placed sutures (fig. 1).

The anterior chamber is reformed with balanced salt solution by placing the anterior chamber irrigator on top of the wound. Then, 100,000 units of soluble penicillin G and 20,000 µg. of streptomycin are injected sub-

TABLE 2
CORNEAL DEGENERATIONS AND DYSTROPHIES
(ETIOLOGIC CLASSIFICATION)

I. DEGENERATION SECONDARY TO:	
A. CHRONIC CORNEAL OR INTRAOCULAR INFLAMMATION	
1. <i>Degeneration in Scars</i> : calcium, lipid, hyalin, and amyloid	
a. Band-shaped keratopathy	
b. White ring of Coats	
c. White limbus girdle of Vogt	
d. Lipoidal dystrophy (? Fuchs' lines of clearing)	
e. Atheromatous ulcer (sequestration)	
2. <i>Pigmentation</i>	
a. Hudson-Staehli line (epithelium)	
b. Atebrin workers	
c. Blood staining (stroma)	
d. Siderosis, chalcosis, & argyrosis (Descemet's)	
e. Krukenberg's spindle (on endothelium)	
3. Pannus degenerativus	
4. Salzmann's nodular degeneration	
5. Glass membrane	
B. SYSTEMIC DISEASE	
1. <i>Epithelium</i>	
Xerosis and keratomalacia	Vitamin-A deficiency
Keratinization and pannus	Pityriasis rubra pilaris
Dust opacities and pannus	Keratos follicularis spinulosa decalvans
Edema and erosions	Epidermolysis bullosa
Pigment (yellow) dots	Chloroquin Rx
2. <i>Bowman's membrane</i>	
Band-shaped keratopathy	Hypercalcemia, Fanconi disease, Rothmund's disease, ichthyosis (also deep keratitis)
3. <i>Stroma</i>	
Keratoconus	Atopic dermatitis
Dot opacities (glycoprotein)	Hurler's gargoylism
Lipoidal dystrophy	Hypercholesterolemia, Schüller-Christian disease
Crystals	Cystinosis, multiple myeloma
4. <i>Descemet's membrane</i>	
Kayser-Fleischer ring (Copper)	Wilson's disease
C. UNKNOWN CAUSES	
Pterygium	
Keratoconus (anterior and posterior)	
Megalocornea and keratoglobus	
Neuroparalytic keratitis	
Posterior embryotoxon	
II. AGING PROCESSES (cornea becomes thinner and flatter)	
Arcus senilis	
Marginal degeneration and Mooren's ulcer	
Cornea farinata	
Hassell-Henle bodies or warts (peripherally)	
Cornea guttata (centrally)	
Fuchs' endothelial-epithelial dystrophy	
Anterior and posterior crocodile shagreen	
III. HEREDITARY	
A. GRANULAR DYSTROPHY (Groenouw's I): dominant, least reduction in vision	
B. LATTICE DYSTROPHY (Biber-Dimmer-Haab, reticular) rare, dominant, reduces vision greatly	
C. MACULAR DYSTROPHY (Groenouw's II) recessive, entire cornea involved, vision reduced greatly	
D. OTHER RARE FORMS OF DYSTROPHY	
Recurrent erosions	
Epithelial (Meesmann, Stocker and Holt)	
Epithelial pitted (Reis)	
Congenital (recessive or dominant, stationary, diffuse)	
Crystalline (Schnyder)	
Deep dystrophy (dominant, blebs on Descemet's membrane)	

conjunctivally. Ordinarily, both eyes are bandaged for one to three days, and mydriatic is instilled on the first postoperative day. The patient is usually allowed out of bed after one to three days.

Sutures are removed approximately three weeks after operation, a somewhat shorter period if healing is expected to be rapid or somewhat later if healing is expected to be slower provided that the sutures appear to be well tolerated without undue necrosis or attraction of blood vessels. For "squeezers," a van Lint injection is given, the pupil is previously dilated widely by Cyclogyl (one percent) and Neosynephrine (10 percent), Diamox is started 24 hours before, and the sutures are removed with Vannias scissors or a razor blade.

CLINICAL RESULTS

KERATOCONUS

It is well known that keratoconus, especially if centrally placed and if the peripheral cornea is of normal thickness, represents one of the best indications for corneal transplantation. This was true of our series (table 3). There were several cases of keratoconus associated with atopic dermatitis, the excellent result following corneal transplantation in one of these patients being shown in Figure 2. This patient returned for an operation on her other eye, which was performed uneventfully and air was injected into the anterior chamber at the close of operation. It

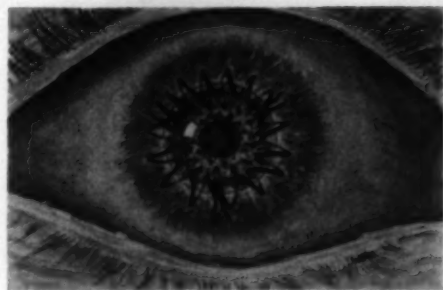


Fig. 1 (Hughes). Showing graft sutured into place with three running silk sutures, initially tied at positions 1, 2, and 3.

has always been a little perplexing why little or no air remains in such eyes after 24 hours, whereas after other operations in which air is injected it will remain for several days. The answer became obvious in this patient in whom by the following day all air had disappeared from the anterior chamber and the iris had prolapsed between two of the closest and most secure appositional sutures. This was immediately excised as shown in the final result (fig. 3). The most reasonable explanation of this complication was that the air and iris were literally forced out of the eye by the air-caused bombé effect so well demonstrated by Scheie in animals several years ago.

In a review of this present series, it was found that most cases of iris prolapse following corneal transplantation occurred in those eyes which had had air placed in the anterior chamber at the close of operation. Since the

TABLE 3
RESULTS OF KERATOPLASTY IN CORNEAL DYSTROPHY

Type.	No. Cases	Clarity of Graft (% Cases)				Change in Vision (% Cases)			Average Follow-Up (mo.)
		Clear	Hazy	Cloudy	Opaque	Better	Same	Worse	
Keratoconus	43	81	14	2	2	95 (3 U)*	2	2 (1 U)*	21
Fuchs	22	55	5	18	22	59 (2.2 U)*	18	23 (2.2 U)*	24
Hereditary	21	67	19	14	0	86 (3.6 U)*	14	0	24

* U = Units or steps in grading visual acuity; viz., 20/15-20, 20/30-40, 20/50-80, 20/100, 20/200, less than 20/200, HM or L.P., No L.P.

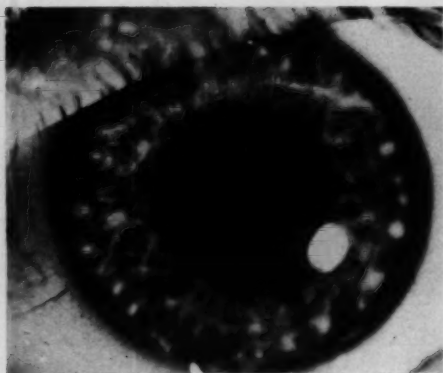


Fig. 2 (Hughes). Graft performed six years previously for keratoconus in a patient with atopic dermatitis.

previously mentioned episode, saline has been introduced into the anterior chamber at the close of operation and, if any leaks appear, additional sutures can be placed. Perhaps balanced salt solution would be even better. With these techniques, the anterior chamber rarely fails to remain formed during the early postoperative course.

Another case of keratoconus, illustrated in Figure 4, had an instructive postoperative

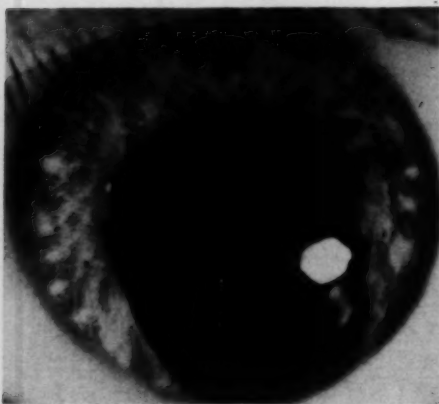


Fig. 3 (Hughes). Other eye of patient shown in Figure 2, four years following corneal transplantation complicated by iris prolapse which was excised. Iris prolapse thought to be caused by air injection into the anterior chamber at the close of operation.

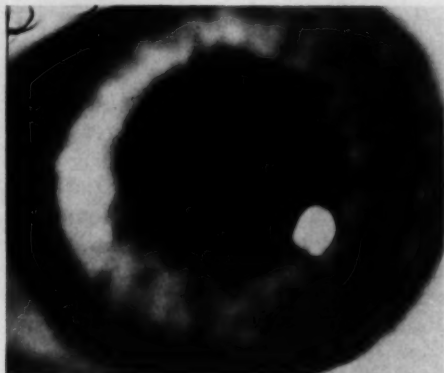


Fig. 4 (Hughes). Keratoconus, preoperatively.

course. A seven-mm. graft was sutured in place using 8-0 nylon (fig. 5). This suture is too fine to be swedged into needles and, therefore, must be tied onto a regular corneal needle. The extreme fineness of this suture makes it more difficult to place and difficult to remove but it causes practically no reaction or necrosis around the suture and does not cut through the corneal tissue readily, as shown in Figure 5 taken six weeks after operation. At the end of 10 weeks postoperatively, the graft was clear (fig. 6). However, the graft showed an alarming absence of healing nasally (fig. 7), but the an-

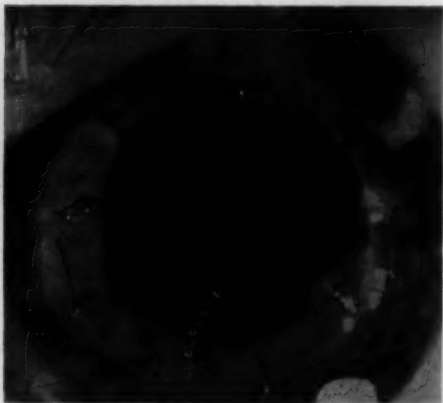


Fig. 5 (Hughes). Same patient as Figure 4, six weeks following corneal transplantation using 8-0 nylon sutures.

terior chamber was never lost. Patient was placed on Diamox and, to the great satisfaction of both the surgeon and patient, the tilting of the graft gradually settled down flush with the host cornea. Five months post-operatively, vision could be corrected to 20/20 by correcting four diopters of myopia and six diopters of astigmatism.

Although it is usual that such cases of tilting or bulging of the graft have higher degrees of myopia and astigmatism, this is not always the case. The use of pressure bandages has been recommended for the treatment of this complication but it seems more likely that it only increases intraocular pressure and, if the eye is turned upward, would accentuate any protrusion or tilting of the graft. Binocular eyepads, however, probably would reduce the blinking reflex and tension on the graft. The most effective therapy is probably reducing the intraocular pressure by a carbonic anhydrase inhibitor.

FUCHS' ENDOTHELIAL-EPITHELIAL DYSTROPHY

This not uncommon senile degeneration of the endothelium with secondary edema of the epithelium and stroma was until several years ago considered untreatable. Stocker first demonstrated successful corneal transplants in early and localized forms of this condition, and at the present time this

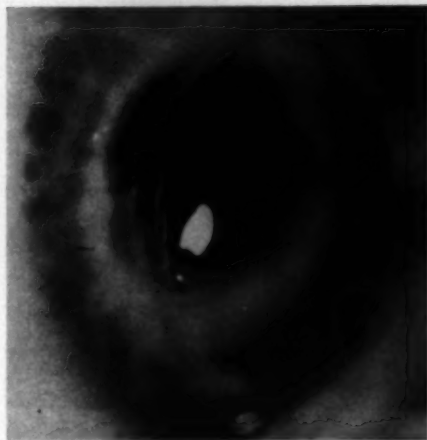


Fig. 7 (Hughes). Lateral view of Figure 6, showing extreme tilting and delay of healing in one quadrant.

condition makes up a large percentage of corneal transplantations. The localized central opacity with relatively normal peripheral endothelium still is the most desirable type of case. However, the dystrophy may be eccentric, as shown in Figure 8, in which the bullae were located in the lower temporal quadrant. The graft in this case was performed somewhat eccentrically, as shown in Figure 9, with a good result and 20/20 vision.



Fig. 6 (Hughes). Same patient as Figure 5, 10 weeks following operation. A small groove is noted down and to the left.

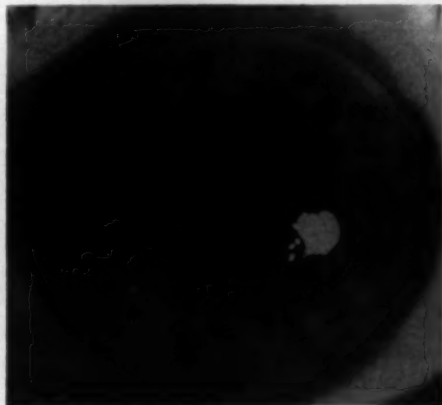


Fig. 8 (Hughes). Eccentrically located Fuchs' endothelial-epithelial dystrophy.

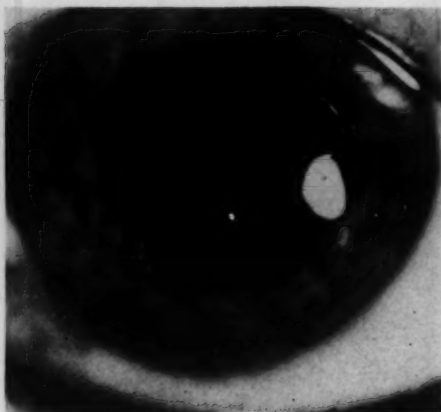


Fig. 9 (Hughes). Same patient as Figure 8, two months following corneal transplantation.

Another patient with Fuchs' dystrophy also had a fine result in her left eye (fig. 10). She returned for an operation on her other eye which was performed uneventfully. However, between the third and ninth postoperative day, the eye showed undue congestion and rather intense iritis, which subsided after the patient was given systemic corticosteroids. The graft remained entirely clear until two months postoperatively when she had another severe attack of ocular inflammation with edema and cloudiness of the graft, considered to be a homograft reaction.

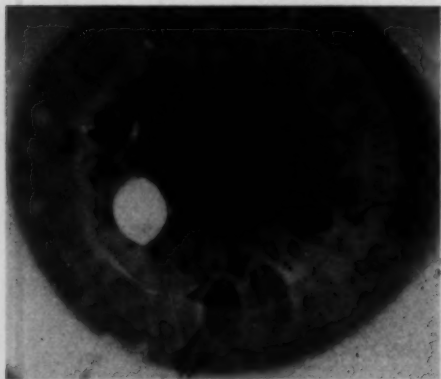


Fig. 10 (Hughes). Fuchs' dystrophy, three years following corneal transplantation.

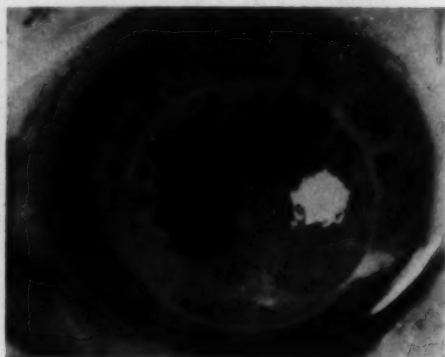


Fig. 11 (Hughes). Other eye of patient shown in Figure 10, 21 months following a corneal transplantation complicated by a late homograft reaction.

After being seen several days later, both systemic and local steroids were given, and the inflammatory component of this reaction subsided but the graft remained cloudy as shown (fig. 11). Another milder attack of inflammation and edema of the graft occurred 20 months postoperatively.

Questions arise as to the best time for operation on cases of Fuchs' dystrophy, and whether any successful results can be obtained in late cases or those with extensive

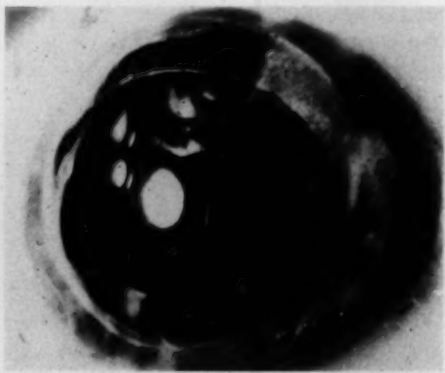


Fig. 12 (Hughes). Far-advanced Fuchs' dystrophy, treated two and one-half years previously by an eccentrically placed eight-mm. penetrating graft combined with multiple peripheral iridectomies. Graft remained clear in spite of extensive peripheral anterior synechias to the posterior surface of the host cornea and wound.

peripheral changes in the endothelium. The patient's cornea shown in Figure 12 had an eight-mm. penetrating keratoplasty for a far-advanced Fuchs' dystrophy one and one-half years previously. At the time of operation vision was limited to counting fingers, the entire epithelium was edematous with bullae, and endothelial changes extended to the periphery. The eight-mm. graft was placed somewhat eccentrically and multiple peripheral iridectomies were performed over one half of the globe. This did not prevent peripheral anterior synechias from forming between the peripheral iridectomies, but these synechias appeared to be adherent to the host cornea and were not included in the lips of the wound. In spite of a mild inflammatory reaction during this second postoperative week which was treated with systemic corticosteroids, the graft remained clear and the tension normal.

Because some relatively late forms of this condition result in clear grafts, the surgeon need not be in such a hurry to operate on those cases with relatively good vision and central changes limited to the endothelium without overlying epithelial edema. The risk of the operation in these very early cases probably outweighs the disadvantage of a later operation at a somewhat more advanced stage of the disease. Accordingly, it might be best to wait until there is definite epithelial edema with reduction of vision be-

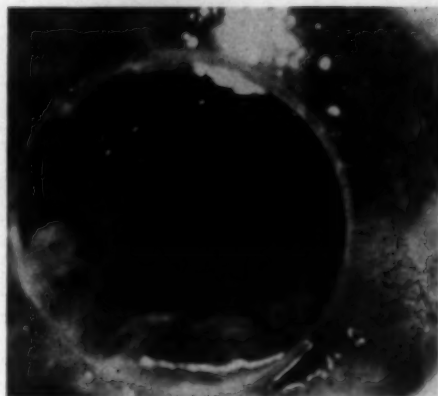


Fig. 14 (Hughes). Same patient as shown in Figure 13, two months postoperatively.

low reading level (for example, 20/70) before corneal transplantation is performed. As seen by the results of 22 cases in Table 3, the promise of success after operation seems encouraging, over half the cases obtaining satisfactory results.

HEREDITARY DYSTROPHY

The diminution of vision resulting from granular dystrophy is usually not disabling, and therefore few of these cases require surgery, none in the present series. However, most cases of lattice and macular dystrophies eventually require a corneal transplantation. Because it is unwise to remove all of the degenerated tissue by an extremely large

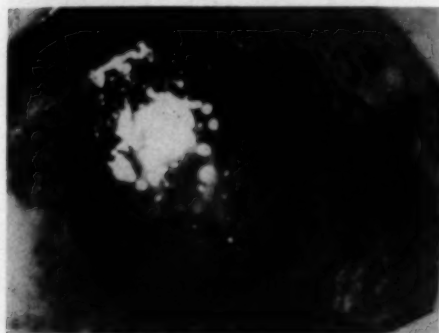


Fig. 13 (Hughes). Lattice corneal dystrophy preoperatively.

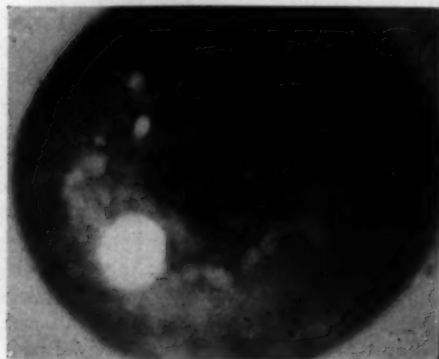


Fig. 15 (Hughes). Macular dystrophy, preoperative.

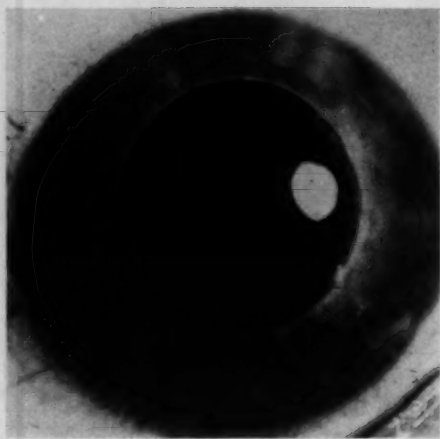


Fig. 16 (Hughes). Same eye as Figure 15, four months following corneal transplantation.

graft, only the most cloudy central portion is removed by a six or seven-mm. graft. The case of lattice dystrophy pictured in Figure 13 was operated on successfully (fig. 14), the only postoperative complication being a mild gutter formation and tilting of the graft. Vision eight months latter was 20/30 with two diopters of myopia and no astigmatism.

A physician's wife with macular dystrophy (fig. 15) was operated. On the 21st postoperative day, the sutures were removed, followed by a loss of the anterior chamber which reformed by the following day. The graft tilted to such an extent that only about one third of the graft was in contact with the host cornea above. On Diamox, the amount of tilting diminished so that her vision could be corrected to 20/40 with a correction of nine diopters of myopia and seven diopters of mixed astigmatism, and 20/20 corrected vision with a contact lens (fig. 16). One year later she returned stating that her eye had become somewhat inflamed and vision had diminished. She was found to have edematous clouding of the temporal one third of her graft associated with the infiltration of blood vessels (fig. 17). Treatment with both systemic and local corti-

costeroids and 1,000 rep of beta radiation resulted in the clearing of this opacity in about two weeks and gradual disappearance of the vascularization (fig. 18). Fortunately, vision was not affected by this apparently localized homograft reaction.

The over-all results of the 21 cases of hereditary dystrophy operated on in this series was good (table 3), 67 percent having entirely clear grafts and 86 percent showing improvement in vision. No cases terminated with an opaque graft or reduction in vision.

LIPID DEGENERATION OF THE CORNEA

Deposits of lipoidal substances and calcium are not uncommon in chronic keratitis. Cases of primary lipid degeneration are seen occasionally, characterized by yellowish-white or gray granular deposits in the corneal stroma. Vascularization and increasing irritability ensue. Some of these cases show hypercholesterolemia.

One 52-year-old man was referred because of progressive reduction in vision of each eye for the previous year. Irregular white opacities were present mainly in the lower two thirds of the corneal stroma with

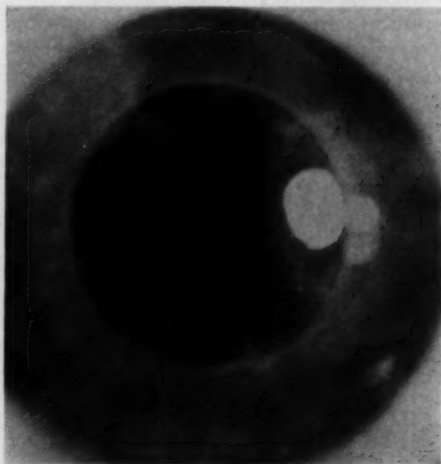


Fig. 17 (Hughes). Same eye as Figure 16, one year after corneal transplantation, showing cloudiness, edema, and vascularization of the right third of the graft.

moderate deep vascularization. A six-mm. penetrating corneal transplantation was performed on the worst eye with a preoperative vision of counting fingers. Postoperatively, the pre-existing vessels ran around the edge of the graft but did not penetrate into it. Corticosteroids were used both locally and systemically. Vision improved to 20/20 with one diopter of myopia and two diopters of astigmatism (fig. 19). One and one-half years later some lipoidal deposits appeared in the lower periphery of the graft but five months later these deposits were hardly visible. Sections of the excised cornea showed the characteristic picture of primary lipid degeneration, with focal corneal necrosis with reactive lipid histiocytosis, vascularization, and chronic interstitial inflammation.

In the past such cases have been considered to be poor risks for corneal transplantation, perhaps because of the deep vascularization by trunk vessels, necrosis of collagen surrounding the graft, and tendency for recurrence of the condition in the graft.

One other patient with a clinical diagnosis of lipoidal dystrophy obtained a clear graft with vision improving from 20/100 to 20/20. A third patient with a keratitis of unknown



Fig. 19 (Hughes). Lipoid degeneration of the cornea, three years following corneal transplantation.

etiology but with lipoidal deposits had a preliminary lamellar graft followed by a penetrating graft which developed a late homograft reaction, so that the graft became edematous and cloudy with no improvement over the pre-operative vision of 10/200.

It would seem, however, worthwhile to operate these cases of lipid degeneration with special attention being paid to preventing vascularization by the use of corticosteroids and postoperative beta radiation if necessary, plus secure suturing to compensate for the possibility of delayed healing if any degenerated stroma is adjacent to the graft.

ROSACEA KERATITIS

This type of vascularizing keratitis of unknown etiology may or may not be a true dystrophy or degeneration. It may be associated with rosacea of the skin and its corneal manifestation may be that of a progressing infiltrate followed by a tongue-shaped sheaf of vessels or a more generalized vascularization.

Those cases which do not respond to the use of corticosteroids locally often clear up after elimination of the corneal vascularization by beta radiation. A small number of cases remain which have residual central scarring, or in which the vascularization is so diffuse, deep, or fine that beta radiation

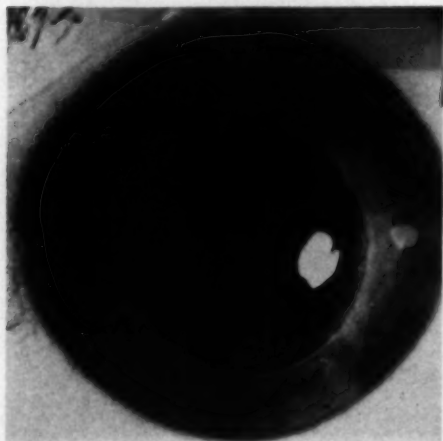


Fig. 18 (Hughes). Same eye as Figure 17, two months after treatment of homograft reaction with local steroids and 1,000 rep of beta radiation.

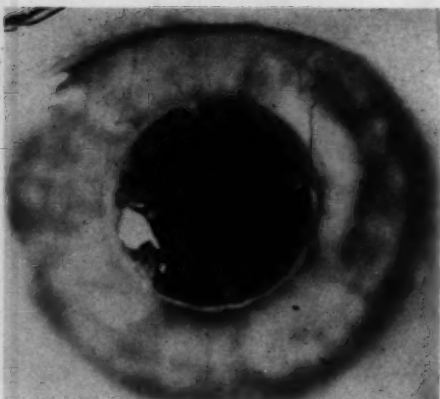


Fig. 20 (Hughes). Rosacea keratitis, three months following corneal transplantation. Vessels have circled but have not entered the graft.

is considered undesirable. Corneal transplantation in these situations has been given a poor prognosis in previous reports of a few cases.

In Figure 20 is shown a 45-year-old woman with a vascularizing keratitis and the vision reduced to counting fingers. A five-mm. penetrating corneal graft was performed. The early postoperative course was essentially uncomplicated except for a loss

of the anterior chamber for two days following the removal of a deeply placed suture. Vision at the end of six months was 20/30 (fig. 20). Seven months postoperatively, she developed a rather severe homograft reaction which subsided on dexamethazone (0.75 mg., q.i.d.) and Metimyd ointment (0.5 percent, t.i.d.) within two weeks. Following this, the vision was 20/40 corrected.

A second case of what appeared to be rosacea keratitis was instructive because of the stormy postoperative course. A five-mm. graft was performed uneventfully using nylon sutures. At the end of three weeks, the pre-existing vessels in the host cornea showed evidence of penetrating the graft in spite of the use of systemic and local corticosteroids. Accordingly, at three weeks and again at four weeks a spray dose (not touching the cornea) of 1,000 rep of beta radiation was given to the temporal area of this right eye. Because contact therapy was not applied, the effective dose was much less than 2,000 rep. Six weeks postoperatively, the eye developed a severe inflammatory reaction with edema and necrosis of the graft and protrusion around the entire periphery (fig. 21). This was treated intensively with systemic and local steroids and two weeks

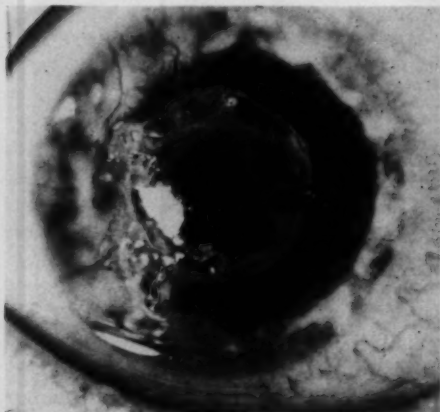


Fig. 21 (Hughes). Rosacea keratitis, seven weeks following a penetrating corneal transplantation, showing an intense homograft reaction with necrosis.

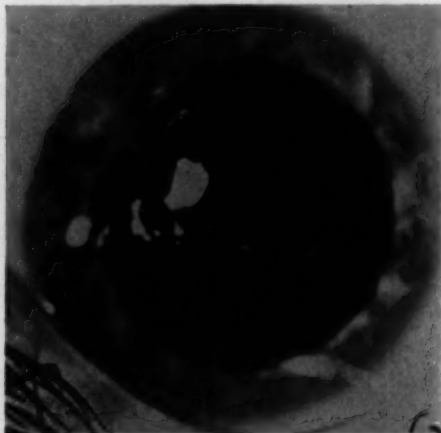


Fig. 22 (Hughes). Same eye as Figure 21, four weeks later, showing remarkable clearing following the use of local and systemic corticosteroids.

later the reaction subsided. The photograph at 11 weeks postoperatively (fig. 22) showed remarkable clearing of the central portion of the graft. The vision at eight months postoperatively was 20/25—corrected with a -12.5D. sph. +6.0D. cyl.

Measures that can be used to reduce the likelihood of vascularization of the graft, especially pronounced in cases of rosacea keratitis, have included the following: (1) heat cauterization at the scleral limbus of large superficial trunk vessels and recession of pseudopterygiumlike tissue, leaving bare sclera at the beginning of transplantation operation; (2) use of as small a graft as possible; (3) measures to reduce the edema of the graft such as careful appositional suturing and Diamox; (4) corticosteroids both systemically and locally; and (5) beta radiation if previous methods are unsuccessful in preventing vascular penetration of the host-graft barrier.

If possible, radiation should be avoided until three or four weeks postoperatively, after which 1,000 rep of beta radiation with the strontium⁹⁰ applicator is usually sufficient to retard these actively growing capillaries. If absolutely necessary one or two weeks later, another similar dose can be applied. Preoperative beta radiation has been discontinued because of its inhibition of healing of the graft (see later) even after doses as low as 3,000 rep, if given shortly before operation, or years later if sufficient radiation has been given to produce ischemia.

MARGINAL DEGENERATION

Three eyes with marginal degeneration were treated by means of irregular grafts by Wilder with good results and these will be reported elsewhere. A fourth case with a severe marginal degeneration around the entire periphery and extending into the sclera, which had been treated by large doses of beta radiation years before, associated with cataract, was treated with a 12.5-mm. graft and later cataract extraction, with no improvement in vision.

One patient with a bilateral Mooren's ulcer was treated on separate occasions with a lamellar graft in each eye, so placed that they overlapped the limbal region to replace as much of the adjacent necrotic sclera as possible. These grafts both became necrotic and sloughed between three and six weeks postoperatively. A third Mooren's ulcer was treated by a lamellar scleral and full-thickness corneal graft. The graft became opalescent, and it seemed that the process of degeneration was taking place at the corneal edge of the graft. There has been only two months follow-up of this patient.

TREATMENT OF CORNEAL OPACITY ASSOCIATED WITH CATARACTS (table 4)

Fuchs' dystrophy and other forms of corneal opacity are not infrequently associated with cataract. Because penetrating corneal transplantation in an aphakic eye is at present fraught with danger of vitreous loss or adhesion to the graft, the usual procedure

TABLE 4
TREATMENT OF CORNEAL OPACITY ASSOCIATED WITH CATARACT

Operation	No. Cases	Clarity of Graft (% Cases)				Change in Vision (% Cases)			Average Follow-Up (mo.)
		Clear	Hazy	Cloudy	Opaque	Better	Same	Worse	
Combined transplantation and cataract extraction	13	31	23	31	15	67	33	0	20
Successful transplantation and later cataract extraction	18	39	39	11	11	61	33	6	26

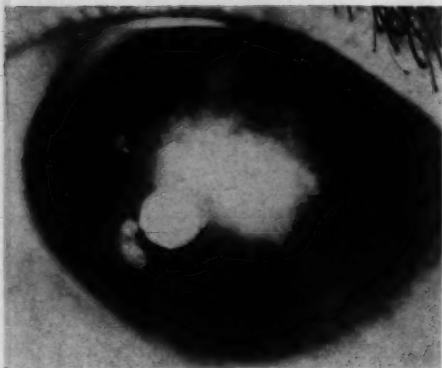


Fig. 23 (Hughes). Corneal scar of dystrophy of unknown etiology combined with senile cataract, preoperatively.

is to perform the corneal transplantation and then follow it six months or so later by a cataract extraction.

Because many of these clear grafts became cloudy after cataract extraction (61 percent in our series of 18 cases [table 4]), a combined transplantation and cataract extraction at one sitting were performed on 13 patients. In these, the technique consisted of a seven-mm. trephination, preliminary placement of four untied sutures from the graft to the host, followed by intracapsular cataract extraction. Despite elaborate precautions, vitreous was lost at the time of operation in three cases.

Others developed adhesion of the hyaloid to the peripheral angle and cornea which did not necessarily lead to cloudiness of the graft. This occurred in the patient shown in Figures 23 and 24 without clouding the graft. This patient also had a homograft reaction three months postoperatively and secondary glaucoma which has been controlled on medical therapy. The results following the combined corneal transplantation and cataract extraction shown in Table 4 are quite comparable to those obtained by a successful transplantation and later cataract extraction. Perhaps the additional trauma to the surgeon doing the combined operation is worthwhile because of the shortened period

of disability and time until the patient regains vision, compared to the two operations separated by an interval of several months.

FACTORS IN HEALING OF THE CORNEAL GRAFT

There are several well-recognized causes of delayed healing of the graft; for example, a poor fit due to faulty cutting or undue thinning of the surrounding host cornea, inadequate suturing, or inclusion of iris between the lips of the wound. It has been our clinical impression that more grafts placed during the past few years have shown evidence of delayed healing such as gutter formation anteriorly, tilting after the removal of sutures, or bulging of the entire graft with resultant high myopia.

Two important differences from the past during these recent years have been the greater number of operations on dystrophies, and the greater use of both systemic and local steroids. These two factors were therefore compared (table 5). It is readily seen that the systemic use of steroids has had no effect on healing of the graft but that dystrophies have a higher percentage of loss of the anterior chamber and evidences of poor healing. Relatively few cases were given



Fig. 24 (Hughes). Same eye as Figure 23, eight months following a combined corneal transplantation and cataract extraction.

steroids locally during the first two weeks after operation and these showed no retardation of healing. Those cases treated later with steroids locally showed a suggestively higher incidence of poor healing, although these cases are probably weighted to include those which were doing badly and so were placed on local steroid therapy.

It has been shown by McDonald and Wilder that beta radiation delays the healing of corneal incisions in rabbits, so this factor was evaluated in this series (table 5a). It would appear that preoperative beta radiation does have a slight inhibitory effect on healing, although such cases necessarily have more severe corneal pathology than the control groups. Certain specific instances of delayed healing in an area of radiation ischemia are too dramatic to be ignored but it is doubtful if less destructive doses of radiation given months or years prior to surgery have much effect on healing. It is also doubtful if small doses such as 1,000 rep given three or four weeks after surgery in those cases in which vessels are penetrating the graft in spite of steroids have any deleterious effect on healing.

RELATION OF CORNEAL VASCULARIZATION, EDEMA, AND HOMOGRAFT REACTION

One of the possible explanations of the low incidence of homograft reactions following corneal transplantation is the avascularity of the recipient site. To test this in the present series, the amount of corneal vascu-

TABLE 5a
INFLUENCE OF PREOPERATIVE BETA RADIATION ON HEALING OF CORNEAL GRAFTS

	No. Cases	Loss of Anterior Chamber (%)	Poor Healing (%)	Anterior Synchias (%)
No radiation				
Avascular host	25	16	52	33
Vascular host	91	14	44	37
Beta radiation	16	44	67	50

larization both pre- and postoperatively was correlated with what is considered to be a homograft reaction, namely, a rather sudden increase in general ocular inflammation, a strongly positive aqueous ray, and edema of the graft. The results given in Table 6 show a negative correlation, that is, the presence of corneal vascularization is associated with a lower incidence of the homograft reaction. As expected in line with Cogan's work, there is a direct correlation between the postoperative invasion of vessels and edema of the graft. Therefore it has been our practice to treat edematous grafts with steroids to combat any allergic homograft component and inhibit vascularization, and to give carbonic anhydrase inhibitors such as Diamox to reduce the intraocular pressure.

CONCLUSIONS

Corneal degenerations and dystrophies now are one of the most common forms of corneal pathology for which corneal trans-

TABLE 5
INFLUENCE OF SYSTEMIC CORTICOSTEROIDS ON HEALING OF CORNEAL GRAFTS

	No. Cases	Loss of Anterior Chamber (%)	Poor Healing (%)	Anterior Synchias (%)
No steroids				
Dystrophies	34	41	82	23
Nondystrophies	53	15	45	31
Steroids				
Dystrophies	50	30	82	24
Nondystrophies	57	16	44	29

TABLE 6
RELATION OF CORNEAL VASCULARIZATION, EDEMA AND HOMOGRAFT REACTION IN KERATOPLASTY

Corneal Vascularization	No. Cases	Homograft Reaction (%)	Edema of Graft (%)
Preoperatively			
None	121	22	33
Present	97	18	45
Severe	32	3	38
Postoperatively			
None	72	25	22
In host only	81	22	36
In graft	95	7	53

plantation is performed successfully. Such cases appear to heal more slowly, probably because of disease in the adjacent host stroma. There is no evidence that the systemic use of corticosteroids inhibits the heal-

ing of corneal grafts. No causal relationship is found between the presence of corneal vascularization and the development of the homograft reaction.

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CONGENITAL HEREDITARY CORNEAL DYSTROPHY*

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The most frequently reported familial corneal dystrophies are those that have been referred to as Groenouw's Type I and II and the Haab-Dimmer type. Franceschetti, et al.¹ have more recently classified these noncongenital and progressive dystrophies as the classical forms. The granular and latticelike degenerations follow a dominant pattern of inheritance and the macular lesions a recessive form. Congenital hereditary corneal dystrophy is another distinct entity that has been thoroughly described in the continental European literature²⁻⁸ but has been infrequently described in the English writings.^{1,9}

Eight patients with congenital hereditary corneal dystrophy have been examined by me. A summary of their histories follows.

CASE HISTORIES

CASE 1

W. C. a white boy. This patient was aged 11 years when first examined on September 26, 1950.

Family history. The patient's parents' eyes were examined and were normal. There was no history of ocular disease in the family and the patient had no siblings.

Present illness. The patient was noted to have corneal opacities at birth. The parents thought the child's visual acuity had decreased only slightly since early childhood. He had had no ocular inflammation or photophobia.

Ocular examination. There was no evidence of nystagmus. The eyes were not inflamed. Corneal sensitivity was essentially normal. The corneas were diffusely hazy. On slitlamp examination there was a slight roughening of the corneal epithelium. The stroma had a ground-glass appearance that was

more marked in the periphery than in the central portion. The peripheral cornea appeared about twice normal thickness. There was no evidence of cornea guttata or endothelial changes in the central portion of the cornea. Neither cornea was vascularized. His corrected vision in the right eye was 20/70 and in the left eye 20/80. Fifty-percent glycerine instilled into the cul-de-sac caused a slight clearing of the cornea and an improvement of visual acuity in the right eye to 20/60 and in the left eye to 20/70. The iris and lens appeared normal. The fundus was not clearly seen but no gross abnormalities were detected. Visual fields were within normal limits. Intraocular pressure was 15 mm. Hg in both eyes (Schiotz).

When the patient was next examined in February, 1954, his visual acuity in each eye was 20/200 (fig. 1). He was able to read 14/14 or J1 at five inches in the right eye and 14/84 or J8 at five inches in the left eye. The patient was given one-half percent carboxymethylcellulose to be instilled three times a day in each eye but this did not improve his visual acuity. On March 15, 1954, an eight-mm. penetrating corneal graft was done on the left eye. The graft healed without complications. There were no adhesions of the iris to the wound and the cornea did not become vascularized. On April 2, he was able to read 20/50 with the left eye and, by April 30, his visual acuity had improved to 20/30 and he was able to read 14/21 (J3) with ease (fig. 2). On May 26 he developed a slight inflammation of his eye and a slight edema of his graft. His visual acuity was reduced to 20/40-. The patient was placed on systemic steroids but, in spite of this, the corneal graft became progressively more opaque and by July 20 his visual acuity was reduced to counting fingers at one foot. The opacification of the transplant did not look like a delayed homograft reaction but rather like an extension of the disease of the recipient cornea into the donor button.

The patient was not seen again until June, 1956, at which time he was 17 years of age. At that time the visual acuity in the right eye was 4/400 and in the left eye he was able to count fingers at two feet.

The right eye was not inflamed. The cornea was definitely more edematous than it had been in the

*From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University. This study was supported, in part, by a grant from the Knights Templar Eye Foundation, Inc.

past. It was still not vascularized. The opacity was greatest in the periphery but there was a diffuse roughening of the epithelium over the entire cornea. The central portion of the cornea was thought to be about twice normal thickness. The graft in the left eye was completely opaque and a few blood vessels were present in the recipient cornea which extended into the corneal graft.

The patient volunteered that the visual acuity in his right eye was definitely worse on cloudy, humid days than it was when the weather was dry and was more blurred when he first awakened than later in the day. Intraocular pressure was normal and the corneal diameter measured 11.5 mm. horizontally in both eyes.

On June 27, 1957, an 11-mm. homograft was done on the left eye. This transplant became opaque.

It is of interest that the mother stated, in 1954, that the child's IQ was 132. He was an honor student in the school for the blind. He attended college in California and made excellent grades.

Histologic examination. The first corneal button removed revealed diffuse irregularity of the corneal epithelium. Bowman's membrane was irregular and absent in some areas. There was a diffuse edema of the corneal stroma. The corneal fibers were evenly separated and did not run in the normal lamellar bundles. The endothelium was distorted from handling of the tissue at the operating table but it appeared essentially normal and there were no excrescences on Descemet's membrane. No nodules were noted in the corneal stroma. Sections of the corneal button were stained with hematoxylin-eosin and periodic acid-Schiff (PAS) stains.

CASE 2

G. H., a white boy, was 20 months of age when first examined on April 1, 1950.

Family history. The parents' eyes were examined and the corneas were normal. The patient had one sister whose eyes were normal. The parents knew of no other member of the family who had ocular disease.



Fig. 1 (Maumenee). Case 1, February 9, 1954.

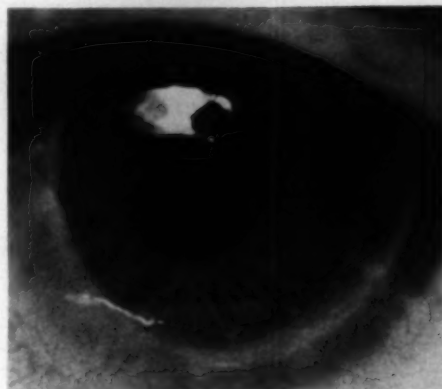


Fig. 2 (Maumenee). Case 1, April 2, 1954.
Clear corneal graft.

Present illness. The mother first noticed a blue discoloration of both corneas at the age of three weeks. She thought the corneal opacities remained approximately the same from that time until the child was first examined. The parents reported that their pediatrician stated the child was entirely normal except for his eyes.

Ocular examination. There was a fine nystagmoid motion of both eyes. The eyes were not inflamed and there was no photophobia. The periphery of the cornea appeared slightly clearer than the central area (fig. 3). The corneal epithelium was roughened and the corneal sensitivity was normal. There was a bluish ground-glass opacification of the stroma and it appeared approximately twice normal thickness. The endothelium could not be seen. The iris and lens appeared to be essentially normal. Intraocular pressure was normal to fingers. Visual acuity could not be obtained because of the child's age.

The patient was seen again in May, 1955. He had developed a superficial ulcer of the left cornea. There was a mild circumcorneal injection in the left eye and photophobia. The right eye was not inflamed. Visual acuity was less than 20/400 in either eye. He could count fingers at four feet. Corneal diameters measured 11.5 mm. in the horizontal meridian. The tension was normal to fingers in both eyes. Slitlamp examination revealed the right

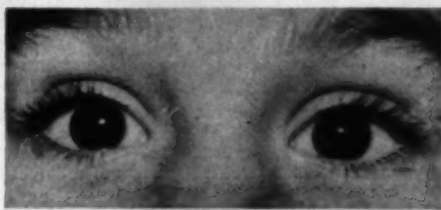


Fig. 3 (Maumenee). Case 2, August 6, 1951.

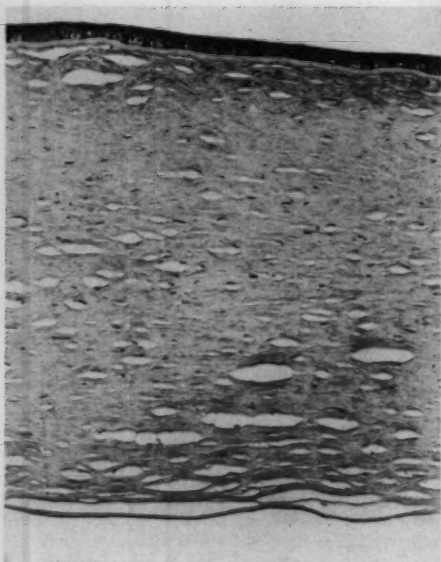


Fig. 4 (Mauumenee). Case 3, corneal button, hematoxylin-eosin, $\times 110$.

cornea to be essentially the same as it was on the first examination. There was no vascularization of the stroma. The left eye showed a small central superficial ulceration of the epithelium. The cornea was not vascularized and the stroma was essentially the same as on the first examination. The patient did not return for an examination after this visit.

CASE 3

W. S., a white man, was first examined in May, 1950, at which time he was 22 years of age. The patient's history was obtained from Dr. Max Fine, San Francisco, California.*

Family History. The parents are living and well. Their visual acuity is normal. The patient had one brother, aged 23 years, with normal vision. There is no family history of ocular abnormalities.

Present illness. The patient gives a history of having had defective vision since birth. He was first seen by Dr. Fine in 1948. At that time his visual acuity in the right eye was 20/200 and in the left eye 20/400. He was able to read 14/21 print by holding it two to three inches from his right eye.

Ocular examination. The patient had a convergence strabismus of approximately five degrees and there was a searching nystagmoid motion of both eyes. The eyes were not inflamed and the patient was not photophobic. There was a diffuse blue-gray homogenous opacity that involved all layers of the corneal stroma. The central portion of the right

cornea was estimated as 1.1 mm. and the left measured 1.3 mm. There was a slight roughening of the corneal epithelium in both eyes and Dr. Fine felt there was some slight irregularity of the posterior surface of the cornea in the right eye. Intraocular pressure was normal in both eyes. Corneal diameter measured 11.5 mm. in the horizontal meridian. The fundi could be dimly seen and the disc and central retina appeared grossly normal. Both corneas were avascular.

On October 20, 1948, a six-mm. penetrating corneal graft was done on the left eye. The immediate postoperative course was uneventful. There were no adhesions of the iris to the back of the wound nor any vascularization of the recipient cornea. The graft remained crystal clear until November 15th, at which time he developed a slight epithelial edema of the graft. This cleared to some extent but the edema became worse by March, 1949. This did not appear to be a homograft reaction. His best visual acuity during the postoperative period in spite of the clear graft was 20/200. In June, 1949, a foreign body became superficially imbedded in his cornea and within three days vascularization developed in the recipient cornea and a bullous keratopathy of the graft. In spite of the use of hypertonic sodium chloride the graft became vascularized and cloudy.

In March, 1950, a six-mm. penetrating square corneal graft was performed. Again this graft became cloudy. In May, 1956, a third graft was done on the left eye. This graft remained fairly clear for about six months but then became completely opaque.

Histologic examination. Sections of the original corneal button were stained with hematoxylin-eosin,

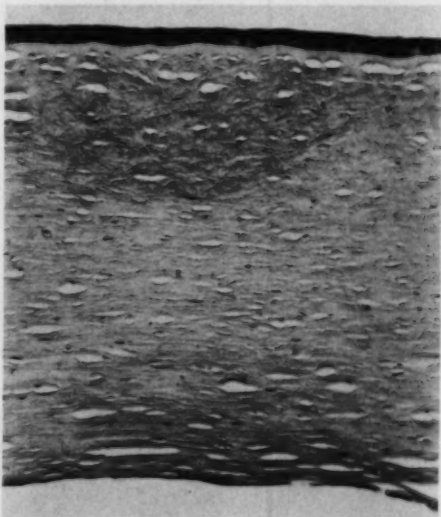


Fig. 5 (Mauumenee). Case 3, corneal button, alcian blue stain, $\times 110$.

* This case is presented through the courtesy of Dr. Max Fine, San Francisco, California.

periodic acid-Schiff (PAS), alcian blue and nuclear red fast, Reinhart-Abul-Haj, Masson's trichrome, toluidine blue, and Weigert's resorcin-fusin stains. Examination of these slides revealed:

The epithelium showed some hydropic swelling of the basal cells but otherwise appeared to be fairly regular. Bowman's membrane was essentially normal. The corneal stroma was diffusely edematous and had a more homogeneous appearance than one normally notes. The corneal edema resulted in swelling of the fibers rather than collection of fluid in the stroma between the corneal bands (figs. 4 and 5). The stromal cells were normal and no hyaline deposits were noted. Descemet's membrane was not thickened. No excrescences were noted on Descemet's membrane but in places there appeared to be a slight duplication of this membrane (fig. 6). The endothelial cells were fewer in number than one would normally expect but this may have been due to the handling of the tissue at the time of surgery. The toluidine blue stains showed a loss of metachromasia probably the result of edema. In the remaining stains the mucopolysaccharides stained normally.

CASE 4

L. M. (JHH 644879) a Negro, was 13 months of age when he was first examined at the Wilmer Institute on July 6, 1953.

Family history. The patient's father died at 38 years of age. His mother recalled that he had a nystagmus but did not think that his corneas were cloudy. A paternal aunt, uncle, grandmother, and cousin had normal eyes. The mother's eyes were normal. The patient had two brothers, aged two and four years, whose eyes were normal and a sister, seven weeks of age, who had congenital hereditary corneal dystrophy.

Physical examination. A physical examination done in the Pediatric Clinic of the Johns Hopkins Hospital revealed the child to be entirely normal except for his eyes. Roentgenograms of the lateral spine, hands, and forearms were negative.

Ocular examination. On August 29, 1959 (essentially the same as July 6, 1953), the patient's eyes were not inflamed or photophobic (fig. 6). The eyes were straight and nystagmus was not noted. Corneal diameters measured 11 mm. in the horizontal meridian. Visual acuity in the right eye was 10/200 and in the left eye 20/200. On slitlamp examination there was a slight irregularity of the epithelium. The stroma appeared diffusely opaque and presented a blue-gray ground-glass appearance. The periphery of the cornea was slightly clearer than the central portion. Corneal thickness measured with the corneal pachometer exceeded 1.0 mm. over the entire cornea. It was difficult to see the posterior portion of the cornea but no gross changes were noted in the form of cornea guttata or endothelial abnormalities. The corneas were not vascularized. The anterior chamber was normal in depth and the lens and iris appeared normal. Corneal sensitivity was normal bilaterally. He was able to read 14/24.5 (J3) in the right eye and 14/51.5 (J4) in the left eye holding



Fig. 6 (Mauensee). Case 4, February, 1959.

the print two inches from his eyes. Finger tension was normal in both eyes. The corneas cleared slightly after instilling 50-percent glycerin into the cul-de-sac.

On October 31, 1959, a nine-mm. lamellar corneal graft was done with dissection of the graft being carried almost to Descemet's membrane. At the time of removal of the lamellar graft, dewlike drops of fluid appeared in the lamellar bed while the superficial cornea was being resected. The corneal graft remained fairly clear for the first two post-operative weeks and then gradually, over a period of the next three to four months, became edematous and completely opaque.

One half of the corneal tissue which was removed was given immediately to Dr. Maurice Langham who calculated the water content of the cornea and commented as follows: "The wet weight of the corneal button was measured immediately after removal from the eye and then placed in an oven and dried to constant weight. From the differences between the values of the wet and dry weights, the water content of the button was calculated to be 70.5 percent. This represents a minimal water content since the cornea would have lost water from evaporation during the time taken to excise the tissue. A closer estimate of the water content was therefore made from the sodium concentration in the excised tissue. The concentration of sodium in the freshly excised tissue was 336 mEq of Na/kg H_2O which is significantly higher than the value of approximately 170 mEq Na/kg H_2O found in the normal rabbit²⁸ and human corneas.²⁹ It is known that the sodium content of the cornea undergoes little, if any, change during swelling and on this basis it may be safely concluded that the sodium concentration of 336 mEq Na/kg H_2O reflected water loss from the tissue during the operation. Consequently, if we assume that the true sodium concentration in the corneal button was 170 mEq, then it may be readily calculated that the true water content was 82.2 percent. A water content of 82.2 percent contrasts to the normal value of 74 to 75 percent and is indicative of a markedly oedematous cornea."³⁰

Histologic examination. The sections were stained with hematoxylin-eosin, periodic acid-Schiff (PAS), alcian blue and nuclear red fast, Reinhart-Abul-Haj, Masson's trichrome, toluidine blue, and Weigert's resorcin-fusin stains. The corneal epithelium was slightly edematous with some edema of the basal layer of cells. Bowman's membrane was diffusely thickened in most areas but in some places it



Fig. 7 (Mauumenee). Case 4, corneal button, periodic acid-Schiff stain (PAS), $\times 110$.

was missing. The corneal stroma was diffusely edematous and the cornea took a homogenous stain. The normal bundles of stromal fibers were not apparent in many regions (figs. 7 and 8). The stromal cells were essentially normal in number and there were no accumulated hyalin or mucoid materials.

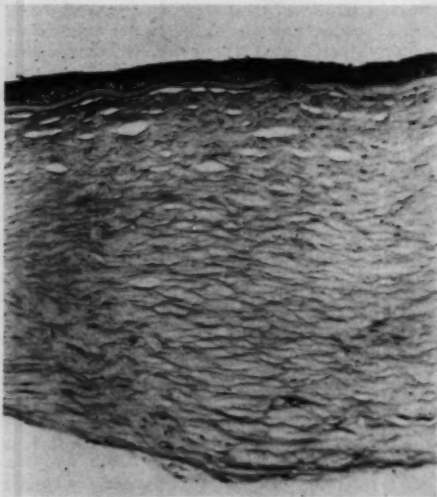


Fig. 8 (Mauumenee). Case 4, corneal button, alcian blue stain, $\times 110$.

Descemet's membrane and endothelium were not present on the slide. There was a loss of metachromasia in the toluidine blue stains but the other mucoid stains appeared normal.

CASE 5

F. M. (JHH 644875) a Negro girl was seven weeks of age when first examined on July 6, 1953.

Family history. Sister to patient in Case 4.

Physical examination. The child was examined in the Pediatric Clinic of the Johns Hopkins Hospital and was found to be normal except for her ocular difficulties. X-ray films of lateral spine, hands and forearms were within normal limits. Serologic tests for syphilis were negative.

Ocular examination. On September 24, 1959, visual acuity in the right eye was 6/200 and in the left eye 8/200 with an isolated E. Intraocular pressure was normal to fingers. The eyes appeared normal externally except for the diffuse corneal opacity (fig. 9). The eyes were straight and there was no nystagmus or evidence of ocular inflammation or photophobia. The ground-glass appearance of the corneal stroma was essentially the same as that described in the previous case. The epithelium was slightly roughened and no cornea guttata could be seen. The anterior chambers were of normal depth and pupillary reactions were entirely normal. The corneas were not vascularized. Corneal sensitivity was essentially normal. Corneal thickness was greater than one mm. in each eye. The corneal diameter was approximately 11 mm. in the horizontal meridian.

CASE 6

P. B. H., a white boy, was two years, nine months of age when examined on May 11, 1960.

Family history. The father, paternal grandparents, three paternal uncles, and one paternal aunt all had normal eyes. The maternal grandparents and one great-aunt and great-uncle all had normal vision. The mother, four maternal aunts, and one maternal uncle all had normal vision. The patient's

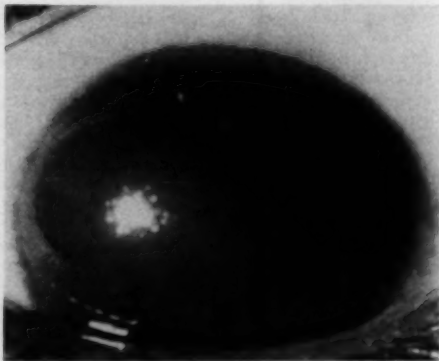


Fig. 9 (Mauumenee). Case 5, December 1, 1958.

mother had two sons by a previous marriage who were in their late teens and had normal corneas. The patient had one full brother, aged five years, with normal eyes.

Physical examination. Neurologic and pediatric consultation on this child revealed no abnormalities other than his ocular findings. Serologic tests for syphilis were negative.

Present illness. The mother stated that the child's corneas were clear until approximately two months of age when they became cloudy. His eyes were not red or inflamed at any time nor did he suffer from photophobia. His intraocular pressure had been checked on three occasions under general anesthesia and his tensions had been approximately 6/5.5 (15 mm. Hg, Schiøtz).

Ocular examination. The eyes appeared straight and there was no noticeable nystagmus. The eyes were not inflamed. Corneal sensitivity was normal and equal on both sides. Corneal diameter measured approximately 11 mm. in the horizontal meridian. The corneas were almost completely opaque and white (fig. 10). On slitlamp examination the epithelium showed a pigskinlike roughening. The stroma was markedly edematous and appeared to be approximately three times normal thickness in all areas from the limbus to the apex. No blood vessels were seen in the peripheral corneal stroma. The opacity of the cornea was so dense that the deeper layers of the cornea could not be seen very clearly. However, the anterior chamber appeared of normal depth and the pupil on transillumination appeared round and responded to light.

CASE 7

J. M.* (JHH 354118) a young white woman was first examined at the Wilmer Institute on June 11, 1945 at which time she was 19 years of age.

Family history. The family history is shown in the pedigree (fig. 11).

Physical examination. This was entirely within normal limits. Serologic tests for syphilis on the patient and her mother were negative.

Present illness. The patient states that her corneas had been opaque since birth. Her visual acuity had remained approximately the same throughout her life.

*This case has been previously reported by Dr. Frank B. Walsh in his book *Clinical Neuro-Ophthalmology*, Baltimore, Williams & Wilkins, 1957, p. 343.

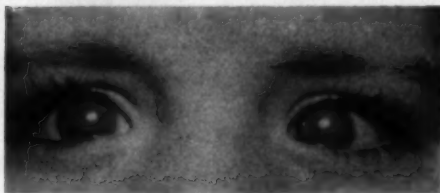


Fig. 10 (Maumenee). Case 6, May 4, 1960.

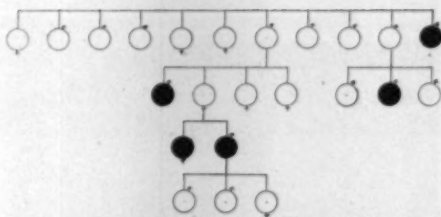


Fig. 11 (Maumenee). Congenital hereditary corneal dystrophy in three generations of one family (Cases 7, 8, and 9).

Ocular examination. On June 11, 1945, the patient's eyes were straight. There was a fine nystagmoid motion of the eyes. Corneal sensitivity was normal and equal on both sides and the eyes were white. The corneal diameters measured 11.5 mm. Intraocular pressure was normal to fingers. On slit-lamp examination the corneal epithelium revealed a slightly roughened appearance. The stroma was diffusely edematous and appeared to be approximately two times normal thickness. The thickening and corneal opacification were greater in the central part of the cornea than in the periphery. There was no vascularization of the stroma. Descemet's membrane was described as thickened but no cornea guttata was noted. The anterior chambers were of normal depth and the pupils round and active in both eyes. Visual acuity was 4/200 with each eye. The corneas did not appreciably clear with the use of five-percent sodium chloride ointment.

On August 8, 1945, a 4.5-mm. square corneal graft was done in the right eye. The graft healed without complications and remained crystal clear (fig. 12). The visual acuity in this eye improved to 10/200 with a refractive correction of -10D. sph. -5.0D. cyl. ax. 20°.

On July 9, 1946, a 4.5-mm. square corneal graft was done in the left eye. This graft became completely opaque. Two subsequent penetrating grafts were done in the left eye and also became opaque.

The patient was last examined on March 11, 1960. The corneal graft in the right eye was still



Fig. 12 (Maumenee). Case 7, March 11, 1960.

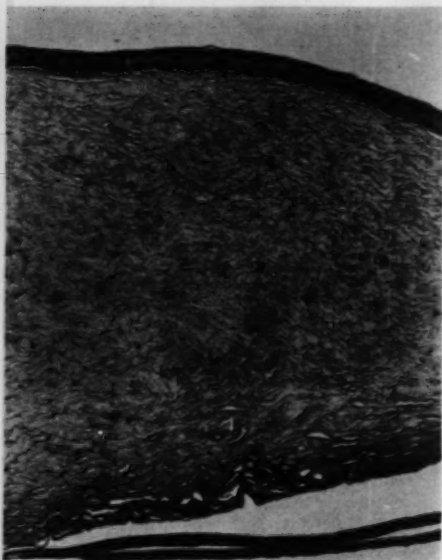


Fig. 13 (Maumenee). Case 7, left eye, alcian blue stain, $\times 80$.

crystal clear and there was a dense corneal scar at the donor-recipient junction. The corneal graft measured with the corneal pachometer about 0.7 mm. in thickness, whereas the recipient stroma measured approximately 0.9 mm. in thickness. Blood vessels were not noted in the recipient cornea. The media appeared sufficiently clear for the patient to have at least 20/40 vision. There were some myopic changes around the optic disc but the disc was of good color. There was some slight pigmentation in the macular area. Visual acuity could not be improved above 20/400 with a -25D. sph. lens. In spite of this, the patient was able to read 14/14 print at four inches with her right eye. She stated that she reads approximately one book a week.

The corneal graft in the left eye was completely opaque and blood vessels extended into the recipient cornea as well as the corneal graft. There were some peripheral anterior adhesions of the iris to the back of the graft in this eye.

Histologic examination. Sections of the initial corneal buttons from the two eyes were stained with hematoxylin-eosin, periodic acid-Schiff (PAS), alcian blue and nuclear red fast, Reinhart-Abul-Haj, Masson's trichrome, toluidine blue, and Weigert's resorcin-fusin stains. The corneal buttons from both eyes appeared to be essentially the same. The epithelium was irregular except for some hydropic swelling in the basal layer. Bowman's membrane was not seen. There was a diffuse homogeneous swelling of the stromal fibers with a loss of the normal corneal bundles and lamellae (figs. 13 and 14). Stromal cells were essentially normal in

number and there were no deposits of hyalin or mucoid material. In the left eye Descemet's membrane was detached but was present on the side. It appeared slightly thickened but this may have been due to an artefact in cutting the material. In the right eye, Descemet's membrane had been peeled off the corneal button. There was a loss of metachromasia in the toluidine blue stained material, probably due to the stromal edema. No other abnormality was noted in the other mucoid stains.

CASE 8

W. M.* (JHH 354126) was first examined at the Wilmer Institute on June 11, 1945, at which time he was 16 years of age. (Date of birth: July 14, 1928.)

Family history. Brother to patient in Case 7.

Present illness. The patient stated that he had had cloudy corneas from birth. His visual acuity varied from time to time and was particularly bad after a long night's sleep or in damp weather. He had had no corneal ulcers or irritation of his eyes. He was able to attend college and obtained a degree in engineering, graduating in the upper half of his class. He has three children, aged three and one-half and two years and three months, all of whom have normal eyes.

General examination. The patient has no physical abnormalities other than his ocular problem.

Ocular examination. (Same on June 11, 1945,

* This case has been previously reported by Dr. Frank B. Walsh in his book *Clinical Neuro-Ophthalmology*, Baltimore, Williams & Wilkins, 1957, p. 343.

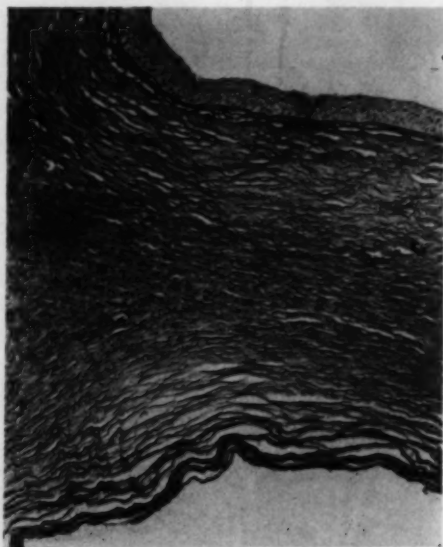


Fig. 14 (Maumenee). Case 7, periodic acid-Schiff stain (PAS), $\times 60$.

and February 11, 1960.) Visual acuity in the right eye was 8/400 and in the left eye 10/400. With contact lens he was able to see 20/300 in the right eye and 20/300 in the left eye. Corneal diameters measured 11.5 mm. horizontally. Intraocular pressure measured 6/5.5 (14 mm. Hg, Schiøtz) in the right eye and 4/5.5 (20.5 mm. Hg, Schiøtz) in the left eye. The patient had a fine nystagmoid motion in both eyes and an internal strabismus of approximately 10 to 15 prism diopters. He preferred fixing with his left eye but was able to fix with either eye. Corneal sensitivity was normal and equal on both sides. The corneas showed a diffuse haze (fig. 15). On slitlamp examination the corneal epithelium was slightly roughened and in a few areas there were a few fine elevations of epithelium that almost looked like bullae. A Hudson-Stahl line was seen just below the pupillary area. The stroma was diffusely cloudy, having a homogenous light gray appearance. It was slightly more opaque centrally than peripherally. The posterior layers of the cornea could be seen fairly well and no cornea guttata was noted. Corneal nerves could be seen entering the central portion but the corneas were not vascularized. The anterior chambers, irises and pupils were normal and the lenses were clear. On ophthalmoscopy only a blurred red reflex could be obtained.

In spite of the fact that the patient stated that his eyes were worse when he first awakened in the morning and that they were better on dry than humid days, his corneas cleared only slightly after the use of hypertonic solutions. It was also interesting that he felt his corneas were clearer after he had worn his contact lenses for several hours than when he first began using the contact lenses. He had worn contact lenses for approximately 10 years and used them for eight to 12 hours a day.

CASE 9

K. S., a white man, age 64 years in 1960. This patient was examined in the Wilmer Institute in 1945 but I have not seen him. He is the uncle of the patients in Cases 7 and 8.

Examination on February 12, 1945, revealed that he had the same type corneal dystrophy as the two previous cases. There was epithelial and stromal edema but no bullae or cornea guttata. The corneas were avascular and normal in diameter. Visual acuity was 5/200 in each eye.

The patient was contacted by mail in March, 1960, and he stated that his eyes had never been inflamed. He was able to read with his right eye by holding print about two inches from his eye. His visual acuity was essentially the same as it had always been. He also stated that his visual acuity was worse when he awakened in the morning than it was by noon. The only other physical abnormality he had was a loss of hearing during the past 10 years.

DISCUSSION

The clinical and pathologic lesions noted in the eight case histories summarized in this

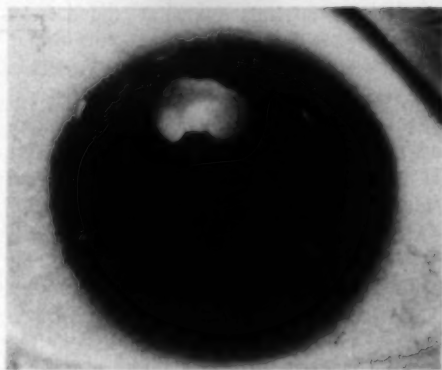


Fig. 15 (Mauensee). Case 8, February 11, 1960.

report are in agreement with those which have been previously described. Congenital hereditary corneal dystrophy as the name implies is usually present at birth but occasionally the parents do not note the lesion until the first month or so of life.

The clinical picture when viewed in its entirety is easily diagnosed but like the classical dystrophies this varies from patient to patient. Thus the corneal opacity is usually stationary but in a few patients it becomes slightly better or worse with passing years. The degree of corneal clouding may vary from almost porcelain white in one patient to only a slight haze in another. Both eyes are usually equally involved by a ground-glass bluish-white opacity of the entire thickness of the stroma. In one patient the periphery of the cornea was more opaque than the apex and in another the periphery was less so. The corneal epithelium is frequently roughened so that it has a pigskin appearance but bullae are rarely seen. In spite of the roughening of the epithelium, corneal staining is infrequent and the eyes are not photophobic or inflamed. In only one eye in this series was ulceration of the corneal epithelium noted. The stroma is diffusely edematous and occasionally contains white dots which may be small water clefts. Cornea guttata has not been observed in Descemet's membrane when this layer could be seen.

The cornea remains avascular and corneal sensitivity is usually normal. Intraocular pressure is normal. Visual acuity varied in this series of patients from 20/70 in one patient to light perception in another. It is noteworthy that in spite of their poor vision five of these patients were able to read without much difficulty. The ages of the patients varied from seven weeks to 64 years.

There are several conditions which may closely resemble this type of dystrophy. These lesions, however, can usually be differentiated without too much difficulty. The first, congenital glaucoma, when present at birth may produce exactly the same type of corneal change but this can be differentiated by the child's photophobia, elevation of intraocular pressure and enlargement of the cornea over a period of months. Birth injury with rupture of Descemet's membrane is more difficult to differentiate unless there are other signs of injury to the child. Intrauterine inflammation may produce an opaque cornea but this is accompanied by other abnormalities of the anterior segment such as peripheral anterior synechias, corneal scars and congenital cataract. The corneal changes in gargoylism (Hurler's syndrome, lipochondrodystrophy) usually do not occur at birth and are almost always accompanied by skeletal abnormalities. Avascular syphilitic interstitial keratitis produces an inflamed eye and subsequent changes in the iris. It also rarely occurs in the first year of life and leaves a scar in the stroma rather than a persistent corneal edema after the active stage.

Histologic examination of the corneal buttons of congenital stationary dystrophy removed at the time of four penetrating and one lamellar transplant showed that the main pathologic lesion was a diffuse edema of the corneal stroma. The excess fluid appeared to be related to a swelling and dispersing of the collagen fibers rather than to pockets of interstitial fluid. Hydropic swelling of the basal layer of epithelial cells and degeneration of Bowman's membrane in some areas were probably secondary to the stromal edema. No

specific changes were noted in Descemet's membrane. The endothelium was not preserved well enough to determine whether it was abnormal or not. The following stains failed to reveal areas of hyalin or mucoid degeneration in the stroma: Toluidine blue, hematoxylin-eosin, periodic acid-Schiff (PAS), alcian blue and nuclear red fast, Reinhardt-Abul-Haj, Masson's trichrome and Weigert's resorcin-fuchsin stains. There was a loss of metachromasia in the material stained with toluidine blue but this was thought to be due to the stromal edema. No abnormalities were noted in the other mucoid stains. The pathologic changes appeared identical in the corneal buttons obtained from patients who had inherited the lesion either by the recessive or dominant mode of inheritance.

The following clinical and laboratory findings suggest that the opacification of the cornea is due solely to edema of the stroma. Maurice has shown that as little as 20-percent swelling of the stroma is sufficient to produce some opacification of the cornea.¹⁴

1. The diffuse clouding of the stroma is very similar to that noted in corneal edema associated with congenital glaucoma, traumatic rupture of Descemet's membrane at birth, or following surgical trauma to the endothelium later in life.

2. The patients frequently stated that their vision was worse after a long night's sleep or on humid days.

3. The cornea clears to some extent, but never completely, after the topical application of hypertonic solutions.

4. The results of lamellar and penetrating keratoplasty closely resemble those after transplants for advanced endothelial dystrophy in that the grafts usually become opaque as a result of gradually increasing edema of the transplant.

5. The changes noted on histologic examination of the cornea are typical of an increase in corneal fluid.

6. Measurements of the degree of corneal hydration in Case 4 were compatible with the amount of corneal swelling and opacification.

If we assume that congenital hereditary corneal dystrophy is due to an abnormal hydration of the cornea from birth, it would be interesting to speculate on the cause of this edema. Two possible mechanisms might be suggested. First, the cornea did not develop properly during embryonic life. If this is so, the reason for the increased water content is not a gross structural change (that is, anterior synechias) as might occur from an intrauterine inflammation for, both clinically and histologically, the cornea appears normal except for the increased fluid in the tissue. Perhaps the change may be due to some alteration in the chemical structure of the stroma that has to do with its state of dehydration. Chemical analysis of corneal buttons has not been done but the PAS, alcian blue, Reinhart-Abul-Haj stains show no abnormal mucoid in the stroma. There was a loss of metachromasia in the sections stained with toluidine blue but this was thought to be due to the stromal edema. Also, an almost total (nine mm.) lamellar transplant down to a few lamellae above Descemet's membrane did not supply enough normal cornea to correct this defect.

The second possibility is that this lesion is a form of congenital endothelial dystrophy. Clinically gross changes in Descemet's membrane in the form of cornea guttata were not observed nor were such changes seen pathologically. Unfortunately, the endothelium was damaged to such an extent in handling the corneal buttons at the operating table that an adequate histologic study of these cells could not be made.

The arguments against this congenital type of edema being a juvenile form of Fuchs' endothelial dystrophy are: (1) the epithelium seldom develops true bullae; (2) the corneal edema is greater in the periphery of the cornea than centrally in some patients; (3) the lesion is usually stationary (note Case 9, patient is now 64 years of age); (4) obvious changes in Descemet's membrane are not seen in most cases. In spite of these dissimilarities to the senile form of

endothelial dystrophy, congenital hereditary corneal dystrophy may be caused by an abnormality in the endothelial cells. This could be an enzymatic defect that altered the normal relations between the limiting membranes (endothelium and epithelium) and stroma. Such a change might prevent the normal deturgescence of the cornea. The answer to these questions must await further studies on the chemical composition of the diseased cornea and on the endothelial cells of these specimens.

Another very interesting finding in these eyes is the total absence of vascularization of the corneas. It has been suggested that the cornea is normally avascular because of the compactness of the tissue due to its state of deturgescence.¹² It has also been suggested that vascular invasion occurs after corneal injury because the corneal stroma becomes edematous in its periphery and thereby reduces the tissue resistance to vascular invasion. An alternative suggestion has been made that the cornea is normally in a state of relative anoxia.¹³ This state of suboxidation calls forth neovascularization but vascular invasion of the cornea is prevented by the compactness of the tissue. Thus, neovascularization will occur if the stroma is edematous near the limbus for a sufficiently long time. The cases of congenital hereditary dystrophy cited in this report do not appear to be compatible with either of these theories.

There is no question that the corneal edema extended to the periphery of these corneas and that it remained for a sufficient period of time to allow vascularization. However, the question remains whether sufficient edema was present to allow vascularization to occur. Since no exact standards have been established for the degree of swelling sufficient to allow vascularization, this question cannot be answered but, from observations on vascularized corneas, it is my opinion that this is the case. It might also be mentioned that in several eyes which became vascularized after graft operations the peripheral cornea did not become appreciably

more edematous at the time when the blood vessels were invading the recipient stroma. Thus, while these cases do not answer the question of why the cornea becomes vascularized after injury they do suggest that the mere presence of edema in the periphery of the cornea is not enough to stimulate neovascularization.

SUMMARY

The clinical and pathologic changes in eight cases (six new) of congenital heredi-

tary corneal dystrophy have been reported. These cases form a distinct entity that must be differentiated from the classical forms of hereditary dystrophy, congenital glaucoma, corneal injury at birth, and avascular syphilitic interstitial keratitis.

The cause of the corneal opacification is a diffuse edema of the corneal stroma. In spite of the fact that this edema extends to the periphery of the cornea vascularization of the stroma does not occur.

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OBSERVATIONS ON RECONSTRUCTIVE AND THERAPEUTIC CORNEAL GRAFTING*

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The dramatic result of penetrating keratoplasty for visual purposes has been well documented, not only in the medical literature but quite extensively in the lay press. Less well known, but still of considerable importance, is the use of corneal grafting for re-

parative or reconstructive need where the initial result is not expected to offer great return in visual acuity but where the major aim is to re-establish or maintain the integrity of the eyeball with the ultimate hope that at a later date more definitive surgery can be employed. Although there is nothing novel in this concept, its potentialities have not been fully exploited. Impetus to such therapy was

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supplied largely by the publications of Paufigue and Sourdille, whose reports began appearing in about 1948. A wave of interest in therapeutic grafting arose but, never reaching very large proportions, has subsequently diminished to a mild ground swell.

It has seemed to me that knowledge in this area is still insecure and that it might be worth while to present my experience with 40 grafting procedures employed primarily for the purpose of either retaining the eyeball or interrupting a disease process in the cornea.

In general the types of disease can be roughly categorized as follows:

1. Vascularized and scarred corneas
2. Deep ulcer or descemetocoele
3. Perforated ulcer
4. Recurrent stromal herpetic keratitis
5. Marginal dystrophy
6. Keratoconus

VASCULARIZED AND SCARRED CORNEAS

The six cases which fell in this group were almost entirely chemical burns. These included sulfur dioxide, sulfuric acid, acetic anhydride and lye. In all, the visual acuity had been greatly reduced to 3/200 or 4/200 and lamellar grafting was performed with the perhaps somewhat naive hope that this, in combination with beta radiation and steroids, might leave a sufficiently avascular bed into which at a later date penetrating keratoplasty could be performed.

It is, of course, well recognized by all those interested in corneal grafting that such eyes offer the poorest prognosis and that in most instances they are doomed to failure. It is a curious fact that occasionally a most unfavorable eye, heavily vascularized at all levels, will upset prediction and present a beautifully clear cornea.

One such situation comes to mind in which a resident, performing his first keratoplasty in an eye which by all of our current standards would probably have been best let alone, succeeded in producing an eye which acquired and retained nearly 20/20 vision.

One can't help but wonder whether some donor tissues are not specifically more acceptable in individual hosts and that the problem is for us to determine what accounts for such specificity. It is not inconceivable that, with further advances in physiology and biochemistry of the cornea, it ultimately will be possible to establish "tissue types" which may be specifically acceptable. At any rate the occasional good result which may occur without benefit of radiotherapy, nitrogen mustards, or steroids gives us hope to continue exploration in this field.

Of the six cases in our group which were heavily vascularized, five were total failures as far as retaining their lack of avascularity was concerned. In one which had a concomitant loss in stroma an increase in thickness was obtained.

DEEP ULCER OR DESCMETOCELE

Clinical management of these conditions can follow no set rule. We are all familiar with severe corneal ulcers and even with small perforating ones that have received no surgical repair and yet have nevertheless proceeded to recovery and eventually a useful eye. However, this happy outcome is difficult if not impossible to anticipate so that in most instances of large, deep ulcers and in descemetocoeles it is my feeling that it is better judgment to intervene surgically before the actual perforation has occurred. Should this happen the subsequent course is indeed complicated.

In the group of 10 such individuals, seven can be considered satisfactory in that the integrity of the globe was retained. One subsequently required enucleation and two were lost to follow-up examinations. In three large sterile ulcers occupying about two thirds of the corneal diameter, lamellar keratoplasties were performed which, while suffering various degrees of opacity and vascularization, nevertheless remained intact and permitted the individuals, although obtaining a maximum visual acuity of only 20/70, to be made comfortable and symptom free.

This type of ulcer has been seen particularly in debilitated chronic alcoholics in whom it has usually been possible to culture gram-negative diplobacilli.³ Small ulcers of this type have usually healed when the individuals were given a normal diet and multivitamin preparations. These have been cases considered primarily trophic disturbances due to faulty nutrition.

Particularly satisfying was a veteran who suffered a severe mustard-gas burn in both eyes during the first World War and who had for the past four to five years been nearly incapacitated with chronic ulceration of one cornea. A 10-mm. lamellar keratoplasty was performed with complete relief of symptoms and with only minimal opacities at the graft-host interface, such that, following removal of a cataract some months later visual acuity of 20/40 was obtained.

Similarly an individual with severe vernal conjunctivitis and recurrent corneal ulcer who had been unable to work for two years became quite comfortable following a large lamellar graft.

A more dramatic, although visually less satisfactory situation, developed in a worker who, in a gasoline explosion, suffered extensive nearly fatal burns of the head and entire body requiring local hospitalization for six weeks prior to first being examined. During this time attention was concentrated on keeping him alive. When I first observed him, both upper and lower lids had suffered such severe cicatricial ectropion that both corneas were totally exposed and necrotic. The anterior chamber of the right eye was present but the left cornea had perforated and cataractous changes were observed.

The patient was immediately removed to the operating room where a 12-mm. lamellar keratoplasty was performed on the right eye and an eight-mm. penetrating keratoplasty was performed on the left, using 6-0 plain catgut suture material. At the same procedure, standard repair of cicatricial ectropion—incision in the skin several mm. from the lid margin, dissection, and removal of sub-

cutaneous scar tissue, tarsorrhaphy, and transplantation of free skin grafts from the supraclavicular area—was performed on both upper and lower lids. The total operative procedure required about six hours.

Because of continued contracture of the subcutaneous scar tissue it became necessary at a latter date to provide additional skin to the lids and, only recently, some three years following the original accident, has it been possible to sever the tarsorrhaphy and observe the ocular status. Although there is considerable scarring in both corneas there is, nevertheless, a reasonable amount of clear tissue left. Bilateral complicated cataracts are present and since light projection remains accurate there are hopes of salvaging some useful vision in this nearly hopeless situation. To date I have had no experience with preserved corneas in clinical conditions. Fortunately, I have been able to obtain fresh donor material in emergencies.

PERFORATED ULCER

Although there is some difference of opinion concerning the handling of descemetocoeles with regard to lamellar versus penetrating keratoplasty, there can be no question that it is technically much simpler to perform a penetrating keratoplasty in an eye that has not perforated than in an eye which has done so. Consequently it is my belief that any except the smallest descemetocoeles are better handled by penetrating transplantation.

Once the descemetocoele has perforated, a decision must be made whether to handle this conservatively or surgically. As a rule, I have felt that those occasional small descemetocoeles, one mm. or so in diameter, which perforate, have a good chance of healing spontaneously. Edema around a perforation of this diameter may be sufficient to plug the wound and, in most instances, healing proceeds uneventfully.

If, in the judgement of the surgeon, the dehiscence is of such a size that edema of the surrounding edges will not be sufficient to obliterate the opening, keratoplasty, pref-

erably penetrating, is in order. On several occasions for technical reasons both in small perforations and descemetocles lamellar grafts have been applied only to find the intraocular fluid diffusing beneath the graft, the iris prolapsing and the graft becoming edematous. The opening has been plugged by anterior synechias and, in these instances, the globe has been retained although not as a visually useful organ.

Descemetocles have also been observed to perforate beneath a previously placed lamellar graft, with a similar end-result. It is, therefore, my feeling that, unless the dissection removes all or nearly all of the necrotic tissue, it is preferable to perform a penetrating keratoplasty uniting sound tissue to sound tissue.

Eight perforating ulcers were encountered in this series. All have done well structurally, although in many instances the grafts became opaque. The visual acuity has depended upon the site of the perforation and state of the remaining ocular structures. With rare exceptions, therefore, I believe that optimal treatment for a perforated corneal ulcer is penetrating keratoplasty. Such exception might be a large perforating *Pseudomonas aeruginosa* ulcer or severe endophthalmitis. In such instances it may be wiser to perform a large conjunctival flap and hope for the best with intensive antibiotic therapy.

RECURRENT STROMAL HERPETIC KERATITIS

Opinion has not yet stabilized on the proper treatment of this condition. All surgeons are familiar with the fact that once herpes simplex has extended past the epithelial stage and has involved stroma, the patient is presented with the probability of a long drawn-out convalescence amounting to months or even years. Periods of relative quiescence are followed by a recrudescence of symptoms. Again, the fact is familiar that, if patience is exercised, most, if not all, of these cases will ultimately become quiet, leaving a greater or lesser corneal scar which, over a period of years, may thin to a con-

siderable degree so that the individual may spontaneously attain quite useful vision. It is because of this that evaluation of therapeutic measures is so difficult.

Therapeutic lamellar grafts have been performed on six of these individuals, five of whom did well in the sense that there was no recurrence of the disease and the patients were immediately made comfortable after months of extreme discomfort. Again, visual acuity depends upon the amount of residual scarring present. One of my cases obtained visual acuity of 20/25. Interestingly enough only recently this patient has had a similar operation performed in the opposite eye after several years of recurring herpetic episodes. The originally operated eye has suffered no further attacks. It would seem that, in some instances, it is necessary to remove the tissue which may harbor a latent virus in order to prevent recurrences.

One unsuccessful case did quite well for a year and then developed a central trophic type ulcer which ultimately perforated. Although the anterior chamber restored and the patient was discharged from the hospital, his final result is not known because he has been lost to follow-up for several years.

It is certain that the final word has not been said in the treatment of this condition. Perhaps a thin conjunctival flap⁴ would be helpful. My current belief, however, is that, if a patient presents with a history of repeated bouts of stromal keratitis, and particularly with ulceration, it is good judgement to perform a lamellar keratoplasty, removing as much tissue as is possible.

MARGINAL DEGENERATIONS OF THE CORNEA

Nine operative procedures in this group were performed on patients in whom it has sometimes been difficult to establish an accurate diagnosis. For example, at times it has been found difficult to be certain whether an individual has a Mooren's ulcer or the marginal degeneration of the cornea which appears in the literature under a variety of names (Fuchs' marginal atrophy or dystro-

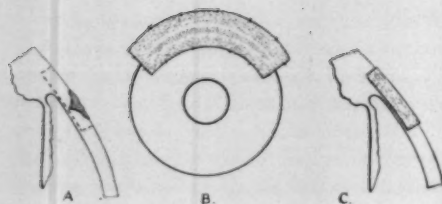


Fig. 1 (DeVoe). Partial ring graft in Mooren's ulcer.

phy, Terrien's dystrophy, peripheral ectasia, and peripheral furrow keratitis). Only three of these nine procedures have been classed as successful but I believe that misjudgment and technical error account for the high degree of failure and that, in most instances, a successful result should be more frequent than my experience implies.

For the purpose of classification, I have considered quiet, noninflammatory, nonpainful peripheral marginal ectasia to be Fuchs' marginal dystrophy and, somewhat clinically similar lesions, associated with pain, inflammation, and redness with usually, but not always, a more rapidly advancing course, to be Mooren's ulcers.

In initial attempts to use ring or partial ring grafts in marginal degenerations, I attempted to match the width of the tissue band removed with a similar width of donor material. I found, however, that the donor tissue retracted after a few weeks, producing a small furrow and leaving very much the situation with which I started.

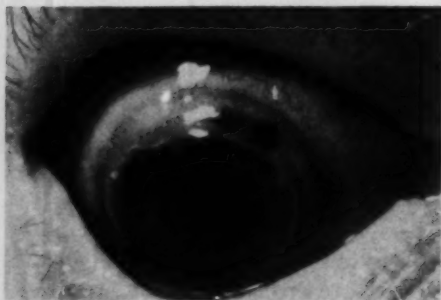


Fig. 2 (DeVoe). Fuchs' marginal dystrophy prior to partial ring graft.

Therefore, in subsequent procedures care was taken to overlap the involved area by several mm. (fig. 1) and the procedure has been utilized successfully since then (figs. 2 and 3).

Severe Mooren's ulcer invading the entire circumference of the cornea has been observed in four eyes of two patients, both Negro. The inexorable progress of the disease has created a serious problem. In all four eyes large "doughnut" types of grafts were performed. In two of these, preparatory dissection of the eye prior to the transferral of the graft revealed the underlying sclera to be soft and almost necrotic for some four to five mm. posterior to the limbus. Because of this the graft was extended to include five to six mm. of adjacent sclera and the "doughnut" was transferred as a sclerocorneal graft.

In three instances these grafts were partially rejected but the eyes ultimately healed with the corneas completely vascularized, only light projection being retained. In the fourth eye, however, a ring-type graft was successfully retained and visual acuity has remained normal without evidence of recurrence of the disease for over two years.

It is realized that on theoretical grounds, operative procedures invading sclera raise the question of how the mechanism of intraocular fluid outflow can be maintained if all subconjunctival connections to the canal of

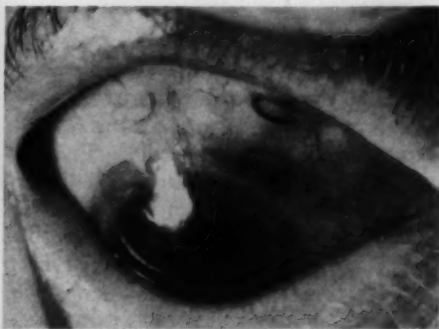


Fig. 3 (DeVoe). Fuchs' marginal dystrophy after partial ring graft.

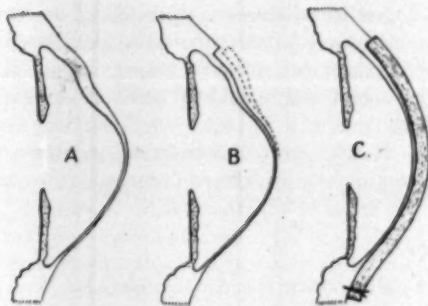


Fig. 4 (DeVoe). Keratoconus with extreme peripheral thinning.

Schlemm system are interrupted. Glaucoma has not developed in these patients, however. I do not hesitate to use corneoscleral grafts over any part of the globe nor indeed over the entire circumference should the clinical situation so warrant.

In spite of uninspiring results with ring



Fig. 5 (DeVoe). Keratoconus with ectasia and acute hydrops.



Fig. 6 (DeVoe). Same patient following 10-mm. lamellar graft.

grafts, I feel that, if properly employed, these offer the best solution to the problem of Mooren's ulcer and peripheral marginal degeneration. It may also be a globe-saving procedure in severe cases of scleromalacia.

KERATOCONUS

Keratoconus is recognized as one of the most satisfactory diseases amenable to keratoplasty, provided thinning of the stroma has not proceeded to the extent that it is impossible to insert suture material. Castroviejo has met the problem of the thin host by using large square grafts, the corners of which extend practically to the limbus. There are times, however, when thinning of the host extends completely to the limbus, as indicated in the sketch (fig. 4-A). Quite satisfactory restoration of the architecture of the cornea can be accomplished by large lamellar grafts, if necessary including several mm. of sclera peripherally (figs. 4-B, 4-C, 5 and 6). When this is done, satisfactory tissue for anchoring sutures in a subsequent penetrating graft is readily obtained.

In an occasional instance, vision can be sufficiently improved by this preparatory procedure to make penetrating keratoplasty unnecessary.

SUMMARY

1. Results of therapeutic corneal grafting in 40 instances have been briefly presented.

2. Such procedures are considered useful in deep ulcer or descemetocoele, perforated ulcer, recurrent stromal herpes, marginal dystrophies and in selected cases of keratoconus.

3. Results are disappointing in vascularized or heavily scarred corneas.

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INTRAOCULAR TRANSPORT OF C¹⁴-LABELED UREA AND THE INFLUENCE OF DIAMOX ON ITS RATE OF ACCUMULATION IN AQUEOUS HUMORS*

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The significance of the observation that the concentration of urea in the aqueous humor is less than in plasma water was recognized first by Dr. Francis Adler.^{1,2} He pointed out that the concentration of substances, like urea, which are neither charged nor utilized, would be equal in blood and aqueous humor if this fluid were the product of dialysis. Adler reasoned that before aqueous humor reaches the anterior chamber it may become so modified that it would no longer be recognized as a dialysate. Time has borne out

the correctness of his view, for although all constituents of aqueous humor appear to enter both the posterior and anterior chambers in part by diffusion (dialysis), that fraction which enters both chambers unidirectionally produces changes which alter the composition from that of a simple dialysate.

Adler and co-workers³ determined the rate of accumulation of urea in the anterior chamber of the cat at various periods after injection of urea and under a variety of experimentally induced conditions. They concluded that deficiency of urea in aqueous was caused by the relative impermeability of the blood-aqueous barrier to urea compared with water, and observed that the barrier breaks down when the intraocular pressure is reduced to zero. The transport of urea, they found, was not under the control of any nervous mechanism.

Davson⁴ also determined the rate of penetration of urea in the anterior chamber of

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cats, and Ross⁵ made a similar study using rabbits. These authors calculated values designated as k_{1a} ; the mathematical formulation employed, however, did not take into account the fact that the rate of accumulation of a substance in the anterior chamber depends not only on its concentration in plasma, but in aqueous of the posterior chamber as well. Concentration of urea in the latter fluid differs significantly from that in plasma and it also varies with time after injection, hence the values calculated as k_{1a} have no readily interpretable meaning. They must vary, too, depending upon the time intervals selected for measuring the concentration.

The present study is concerned chiefly with turnover of urea in the posterior and anterior chambers of rabbit eyes and eyes of rabbits following systemic administration of Diamox. The effect of Diamox on the transport of urea was investigated because of its ability to alter one of the parameters (flow) of the system regulating transport into the intraocular fluids. Pitressin has been shown to affect transport of urea across the kidney tubules^{6,7} and toad bladder,⁸ therefore, its effect on the rate of accumulation of urea in the aqueous humors has also been studied.

METHODS

Young adult albino rabbits (1.8 to 2.3 kg.) were injected with 6.0 microcuries of C¹⁴-labeled urea, 30 percent of which was given intravenously and the remainder intraperitoneally. To maintain the plasma level approximately constant 10 percent of the total initial dose of urea was given intraperitoneally at 45-minute intervals.

In experiments using Diamox, 50 mg./kg. of a 2.5-percent solution was administered intravenously 30 minutes before giving urea and, in experiments involving steady-state, half this dose was given intraperitoneally at two-hour intervals thereafter over a period of 26 hours.

Pitressin, when used systemically, was injected intramuscularly (five units per rabbit) 30 minutes prior to administration of

urea. When it was given intravitreally one-half unit in 2.0 microliters of saline was injected into one eye with a microsyringe (Hamilton Co., Whittier, Calif.) and isotonic saline alone was injected into the contralateral eye to serve as a control, both from three to 25 minutes before giving urea.

Samples of aqueous humor were collected in micropipettes by methods described earlier;⁹ using an 18-gauge needle, vitreous humor was withdrawn into a syringe immediately following death of the animals. Three or more samples of blood were obtained from each rabbit by cardiac puncture.

A thin window flow-gas counter was used to determine radioactivity. Self-absorption corrections were determined for plasma and aqueous and vitreous humors and applied appropriately.

Steady-state ratios of concentration of urea in aqueous of the posterior and anterior chambers were determined on Nelson-Somogyi filtrates from chemical analyses of the fluids using the diacetyl monoxime method of Friedman.¹⁰

MATHEMATICAL CONSIDERATIONS

Coefficients for diffusion across ciliary processes and iris and the concentration of urea in the fluid entering the posterior chamber by secretion were evaluated by selecting values, which when used to draw theoretical curves relating accumulation of urea in the posterior and anterior chambers to time, produced good fits to the experimental data. Theoretical curves were calculated on the basis of an hypothesis previously described in detail,^{11,12} in which it was assumed that substances enter both posterior and anterior chambers by diffusion or by flow, or by a combination of the two. The term secreted fluid was used to describe that fluid which entered the posterior chamber by flow (unidirectionally), but no a priori assumption was made either as to location of the secreted fluid in the ciliary process or the mechanism of its formation. Fluid was presumed to flow from posterior to anterior chamber, and dif-

TABLE 1
MEANING OF SYMBOLS AND UNITS

Symbol	Designation	Units*
A_{hv}	Area of posterior chamber—vitreous interface	cm. ²
α	Donnan factor	Dimensionless
C_a	Concentration in aqueous humor of anterior chamber	Relative units* or mM/Kg. H ₂ O
C_h	Concentration in aqueous humor of posterior chamber	Relative units or mM/Kg. H ₂ O
C_p	Concentration in plasma	Relative units or mM/Kg. H ₂ O
C_s	Concentration of secreted fluid	Relative units or mM/Kg. H ₂ O
C_v	Concentration in vitreous humor	Relative units or mM/Kg. H ₂ O
D	Diffusion constant	cm. ² /min.
$k_{d,lp}$	Transfer coefficient by diffusion posterior chamber to plasma	min. ⁻¹
$k_{d,hv}$	Transfer coefficient by diffusion posterior chamber to vitreous	min. ⁻¹
$k_{d,pa}$	Transfer coefficient by diffusion plasma to anterior chamber	min. ⁻¹
$k_{d,ph}$	Transfer coefficient by diffusion plasma to posterior chamber	min. ⁻¹
$k_{d,vh}$	Transfer coefficient by diffusion vitreous humor to posterior chamber	min. ⁻¹
k_{fa}	Transfer coefficient by flow into and out of anterior chamber	min. ⁻¹
k_{fh}	Transfer coefficient by flow into and out of posterior chamber	min. ⁻¹
V_a	Volume of anterior chamber	cm. ³
V_h	Volume of posterior chamber	cm. ³
V_v	Volume of vitreous	cm. ³
x	Space variable	cm.

* A relative unit is defined as a percentage of the concentration in the plasma once the concentration reached in the plasma is essentially constant.

fusional exchange to take place between blood and posterior chamber across the ciliary epithelium and between blood and anterior chamber across the anterior portion of the iris. Exchange or flux across the cornea was neglected, but exchange of substances between posterior chamber and vitreous and lens was taken into account by mathematical treatment which, unlike earlier methods, did not require the unrealistic assumption that vitreous humor (or lens*) is well mixed. The vitreous chamber was treated as though it were a cylinder having a cross sectional area equal approximately to that of the interface between the posterior chamber and vitreous humor.

Discrete stations were chosen at points equally spaced throughout the vitreous, and by means of an analog computer the concentration at each of these stations was calculated by solving a system of simultaneous partial differential equations which relate time, concentration, and distance in the vitreous from the posterior chamber-vitreous interface.

Equations (1) and (2) were employed to

calculate theoretical rates of accumulation of substances in posterior and anterior chambers, respectively, where C_v in the last term of equation (1) is the concentration at the station next to the interface between posterior chamber and vitreous as generated by the computer.

$$\frac{dC_h}{dt} = k_{fh}(C_a - C_h) + k_{d,ph}(C_p - \alpha C_h) - \frac{DA}{\Delta x V_h} [C_h - C_v]_{x=0} \quad (1)$$

$$\frac{dC_a}{dt} = k_{fa}(C_h - C_a) + k_{d,pa}(C_p - \alpha C_a) \quad (2)$$

The meaning of symbols and units used above and elsewhere in this paper is given in Table 1.

Equation (1) indicates that rate of change of concentration of a substance in the posterior chamber is equal to the flow rate times the difference in concentration between the "secreted" fluid and that in the posterior chamber, plus the diffusion rate times the difference in concentration in plasma water and the effective* concentration in posterior

* Loss to the lens was lumped with that to the vitreous.

* Effective concentration here means that concentration which is operative when corrected for the Donnan effect.

aqueous, minus diffusional loss to vitreous humor. The latter, in turn, is equal to a factor composed of the diffusion rate of the substance within vitreous humor, times area of the posterior chamber-vitreous interface, divided by thickness of vitreous in the first station, times volume of the posterior chamber, all multiplied by differences in concentration between posterior chamber aqueous and vitreous humor in the first station.

Equation (2) says that rate of change of concentration of a substance in the anterior chamber is equal to the flow rate times the difference in concentration between posterior and anterior aqueous plus the diffusion rate times the difference in concentration in plasma water and effective concentration in the anterior chamber aqueous.

Concentrations in posterior chamber aqueous (C_h) and plasma water (C_p) are known at all times from experimental observations; those for the first station in the vitreous (C_v) are obtained as described above by computation. Flow rate (k_{ph}) in normal rabbit eyes is known from independent experimental data (perfusion, tonography,¹³ and turnover of para-aminohippuric acid¹⁴) to be approximately 3.5 μ l per minute; this is equivalent to about six percent and 1.3 percent per minute of the volume of posterior and anterior chambers, respectively. For a non-charged substance like urea, α (Donnan coefficient) is equal to one. Volume of the posterior chamber (V_h) has been estimated from studies of histologic sections to be about 0.055 ml.,¹⁵ area of the posterior chamber-vitreous interface to be 1.2 cm.², and the diffusion rate through vitreous (D) is assumed to be the same as through a salt solution having the same concentration as the vitreous humor, and was taken to be 0.71×10^{-3} cm.²/min.¹⁶

The two unknowns in equation (1) are C_s , concentration in the secreted fluid and $k_{d,ph}$, the value for the diffusion coefficient. While only one equation is available to evaluate these terms, it is possible to determine their magnitude from the known concentra-

tion in posterior aqueous and plasma at steady-state because they bear a fixed relation to each other.

In previous papers^{11,12} the relationship between $k_{d,ph}$ and C_s (for Na and Cl) was calculated on the assumption that their concentration was equal in vitreous and posterior chamber aqueous at steady-state, that is, that there is no net gain or loss to the posterior chamber. However, concentration of urea in vitreous humor under steady-state conditions was found to be 83 percent while that in posterior chamber aqueous is but 72 percent of that in plasma water (table 3). This difference in concentration between vitreous and posterior chamber aqueous must give rise to a net transport of urea from vitreous to posterior chamber at steady-state and so has to be considered in establishing relationship between $k_{d,ph}$ and C_s . To determine this relationship it is necessary to evaluate

$$\frac{DA}{\Delta x V_h} (C_h - C_v)_{ss}$$

at steady-state, that is, when

$$\frac{dC_h}{dt} = 0.$$

This requires information concerning rate of transport of urea from the vitreous to posterior chamber under steady-state conditions.

Rate of transport of urea from vitreous to posterior chamber at steady-state was determined by a procedure identical to that described by Maurice¹⁷ except that analytical data obtained from aqueous sampled from posterior as well as anterior chamber were employed in the calculations. C¹⁴-labeled urea was introduced into the center of the vitreous with a microsyringe and concentrations in vitreous, posterior and anterior chamber aqueous were determined at intervals thereafter. Steady-state is reached in posterior chamber aqueous (crosses) within about one hour and in anterior chamber aqueous (filled circles) after approximately five hours (fig. 1). The transfer coefficient $k_{d,vh}$ can be calculated by Maurice's method¹⁷ from equation (3) using ratios of concentration at steady-

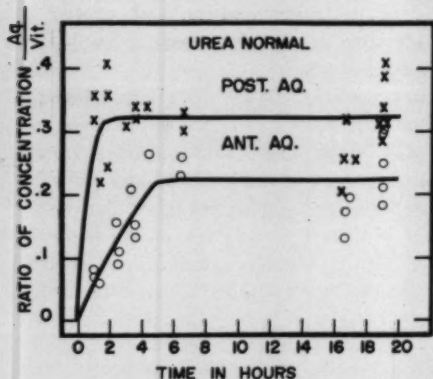


Fig. 1 (Kinsey, Reddy and Skrentny). Ratio of concentrations of C^{14} -labeled urea in the posterior and anterior aqueous after intravitreal injection.

state and k_{out} of the posterior chamber, where $k_{out} = (k_{fb} + k_{d,ph})$.

$$k_{d,vh} = (k_{fb} + k_{d,ph}) \frac{C_h V_h}{C_v V_v} \quad (3)$$

The value of $k_{d,vh}$ is found to be equal to 0.0013.* The values used for solving equation (3) are the same as those employed heretofore, except for $k_{d,ph}$ which was obtained by successive approximation, and are as follows:

$$V_h = 0.055 \text{ ml}; V_v = 1.4 \text{ ml}; k_{d,ph} = 0.036 \text{ min.}^{-1}; \\ k_{fb} = 0.06 \text{ min.}^{-1}$$

Rate of transfer between posterior chamber and vitreous ($k_{d,hv}$) is related to that describing transfer in the reverse direction by equation (5) and has a value of 0.033 min.^{-1} .

$$k_{d,hv} = k_{d,vh} \frac{V_v}{V_h} \quad (5)$$

* Approximately the same value, namely 0.0014 is obtained for rate of transfer from vitreous to posterior chamber when the rate is calculated from anterior chamber data using equation (4).

$$k_{d,vh} = (k_{fa} + k_{d,pa}) \frac{C_a V_a}{C_v V_v} + k_{d,ph} \frac{C_h V_h}{C_v V_v} \quad (4)$$

where $k_{d,pa} = 0.010 \text{ min.}^{-1}$; $k_{fa} = 0.013 \text{ min.}^{-1}$; $V_a = 0.25 \text{ ml}$

This equation differs from that used by Maurice only in that it contains an added term which describes diffusion out of the posterior chamber into plasma.

This rate coefficient can now be used along with known difference in average concentration of urea in the posterior chamber and vitreous under steady-state conditions to evaluate the last term of equation (1) as indicated in equation (6). The difference in concentration is 11 relative units (table 3).

$$k_{d,hv}(C_h - C_v) = \frac{DA}{\Delta x V_h} [C_h - C_v]_{x=0} \quad (6)$$

The value for net transport from vitreous to posterior chamber at steady-state is equal to 0.36 relative units per minute: It is interesting now to observe that the value for C_v in the right-hand term of equation (6), that is, concentration at the first station in the vitreous, is equal to approximately 75 relative units. Thus the difference in concentration $(C_h - C_v)_{x=0}$ is but three relative units, whereas the average difference in concentration in posterior chamber aqueous and vitreous is 11 relative units. This is in accord with the idea that there is probably a concentration gradient extending from the part of the vitreous nearest the retina to the vitreous-posterior chamber interface.

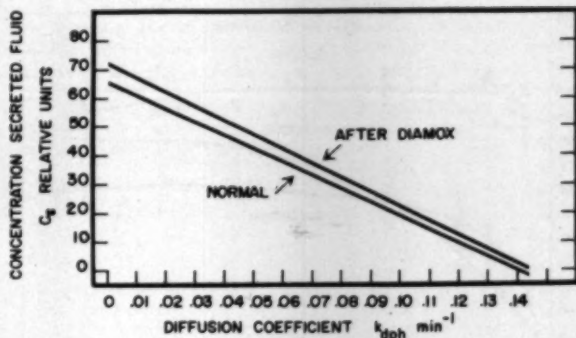
The relation between C_a and $k_{d,ph}$ can now

be computed by setting $\frac{dC_h}{dt}$ in equation (1)

equal to zero and substituting 0.36 for the last term. This relationship is shown by the lower line of Figure 2 for untreated animals and by the upper line of the figure for rabbits given Diamox repeatedly over a period of 26 hours. In the latter instance relative concentrations of urea in posterior chamber aqueous and vitreous at steady-state were found by chemical analysis to be 85 and 97 percent, respectively, of plasma water (table 2). The relationship between C_a and $k_{d,ph}$ for animals given Diamox was calculated on the assumption that rate of diffusion (D) across the posterior chamber-vitreous interface was not altered by the drug.

Various values of $k_{d,ph}$ were then selected, and with appropriate values for C_a , curves were drawn using an IBM 704 Digital Com-

Fig. 2 (Kinsey, Reddy and Skrentny). Relation between concentration of urea in the secreted fluid and the coefficient of diffusion between plasma and posterior chamber aqueous in normal and Diamox-treated rabbits.



puter until a good fit to the experimental data was obtained.

RESULTS

Concentration of C^{14} -labeled urea in the posterior and anterior chambers and plasma of untreated rabbits at various times following parenteral administration, is shown in Figure 3. Each cross and open circle represents concentration in the aqueous of the posterior and anterior chamber, respectively, except the cross and circle showing concentration at steady-state, in which instances the values represent average concentration in eight eyes. The line indicating concentration in plasma is drawn as a visual fit to the data, and the lines through data representing aqueous samples are computed on the basis of equations (1) and (2) using the values for

flow rates, diffusion coefficients, and concentrations in the secreted fluid (C_s) shown in Table 2.

Results in animals which were given Diamox are presented in Figure 4. In this instance too, the curves are theoretical and are calculated on the assumption that Diamox has reduced flow by 50 percent (table 2). Experimental evidence for the validity of the assumption has been reported by Becker and co-workers.^{18,19} Comparison of Figures 3 and 4 shows that rates of accumulation of urea in both chambers are substantially greater in animals given Diamox.

If the theoretical rate of accumulation of urea after Diamox is calculated on the assumption that flow has not been reduced it can be shown readily that the theoretical curves lie well below the experimental data.

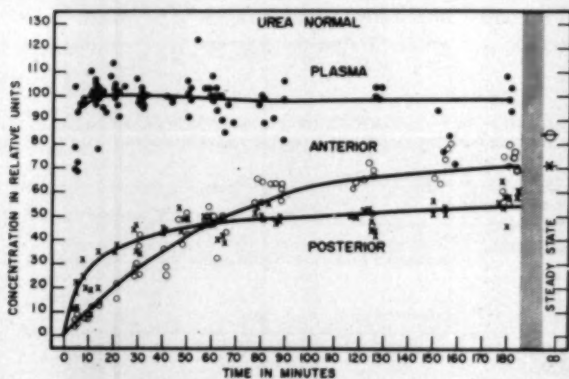


Fig. 3 (Kinsey, Reddy and Skrentny). Concentration of C^{14} -labeled urea in the plasma, posterior and anterior chambers of normal rabbits after parenteral administration.

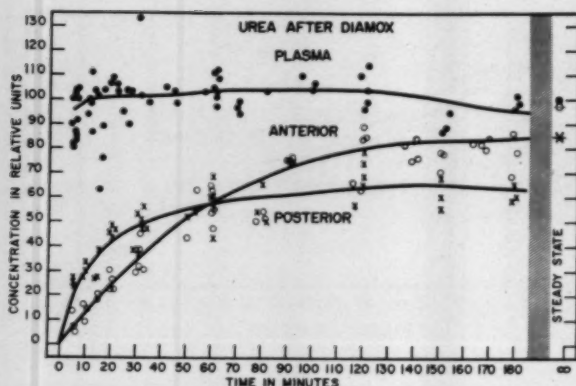


Fig. 4 (Kinsey, Reddy and Skrentny). Concentration of C^{14} -labeled urea in the plasma, posterior and anterior chambers of Diamox-treated rabbits after parenteral administration.

Table 3 shows that steady-state ratios in posterior and anterior aqueous and vitreous humors are also significantly increased by Diamox. This elevation in concentration of urea in the ocular fluids could not be attributed to falling concentration of urea in the plasma at the time the samples were taken, since the concentration in the plasma was shown to be essentially constant over a period of several hours prior to withdrawing the aqueous and vitreous. All of the results, therefore, are compatible with the idea that Diamox increases diffusion of urea between plasma and aqueous of both posterior and anterior chambers. Table 2 shows that the diffusion rate doubles in the posterior chamber, and increases by approximately one and one-half times in the anterior chamber as a result of Diamox.

To illustrate the effect produced by small changes in the values of the parameters $k_{d,ph}$

and $k_{d,pa}$ on the theoretical rates of accumulation of urea, a series of curves were drawn using values for the parameters above and below those shown in Table 2. The results are shown in Figures 5, 6, 7, and 8 in comparison with the curves in Figures 3 and 4 (broad lines). While some of the data could be represented by curves drawn on the basis of elevated or reduced values of the diffusion coefficients as well as those shown in Figures 3 and 4, the latter curves appear to provide better fits to the data as a whole, and the diffusion coefficients reported can probably be considered reliable to within plus or minus 25 percent.

The data presented in Tables 4 and 5 indicate that rate of accumulation of urea in posterior and anterior chambers is not affected significantly by either the systemic or intravitreal administration of pitressin. These results are in contrast to those obtained by

TABLE 2

COEFFICIENTS OF TRANSFER BY DIFFUSION AND FLOW IN THE POSTERIOR AND ANTERIOR CHAMBERS AND THE CONCENTRATIONS OF UREA IN THE SECRETED FLUID ENTERING THE POSTERIOR CHAMBER WHICH WERE FOUND TO PRODUCE A FIT TO THE EXPERIMENTAL DATA BEFORE AND AFTER DIAMOX

	Posterior Chamber			Anterior Chamber	
	Diffusion	Flow	Concentration Secreted Fluid	Diffusion	Flow
Rabbits	$k_{d,ph}$ min. ⁻¹	k_{fb} min. ⁻¹	C_s Relative Units	$k_{d,pa}$ min. ⁻¹	k_{fa} min. ⁻¹
Normal	0.036	0.060	50	0.010	0.0130
After Diamox	0.072	0.030	36	0.014	0.0065

TABLE 3

UREA STEADY-STATE RATIOS IN THE INTRAOCULAR FLUIDS IN NORMAL AND DIAMOX-TREATED RABBITS

Posterior Aqueous		Anterior Aqueous		Vitreous Humor	
Plasma		Plasma		Plasma	
Normal	After Diamox	Normal	After Diamox	Normal	After Diamox
0.73	0.84	0.87	0.96	0.80	0.99
0.71	0.85	0.85	0.99	0.80	0.95
0.70	0.97	0.85	0.98	0.79	0.95
0.72	0.80	0.82	0.97	0.79	0.94
0.74	0.77	0.84	0.90	0.92	1.03
0.73	0.86	0.83	1.02	0.93	0.94
0.71	0.86	0.81	1.01	0.82	0.94
0.71	—	0.84	—	0.81	—
AVERAGE 0.72±0.013 0.85±0.059*		0.84±0.018 0.97±0.037		0.83±0.054 0.97±0.033	

* Standard deviation. The differences in concentration between normal and Diamox injected animals are all significant. $P < 0.01$.

Fig. 5 (Kinsey, Reddy and Skrentny). Theoretical rate of accumulation of C¹⁴-labeled urea in posterior chamber aqueous of normal rabbits for three different assumed values of diffusion coefficient.

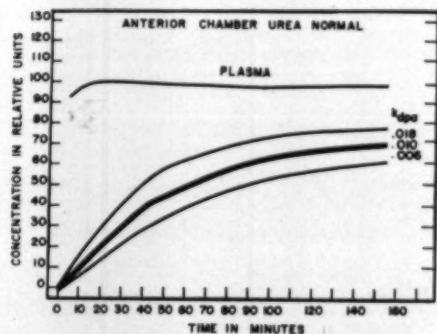
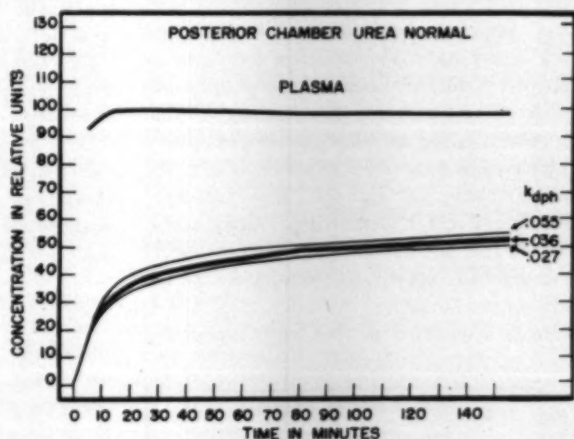


Fig. 6 (Kinsey, Reddy and Skrentny). Theoretical rate of accumulation of C¹⁴-labeled urea in anterior chamber aqueous of normal rabbits for three different assumed values of diffusion coefficient.

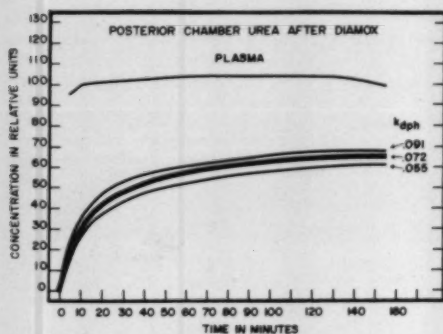


Fig. 7 (Kinsey, Reddy and Skrentny). Theoretical rate of accumulation of C^{14} -labeled urea in posterior chamber aqueous of Diamox-treated rabbits for three different assumed values of diffusion coefficient.

Leaf² who has shown that the transport of urea across the toad bladder is increased as much as 40fold in both directions upon addition of pitressin to the bathing media. Moreover, while the ciliary processes appear to have some properties in common with the kidney tubule, for example, they are capable of actively transporting iodopyracet,²⁰ they do not, at least as far as urea transport is concerned, appear to be affected by the antidiuretic hormone.

Results reported in this paper show that

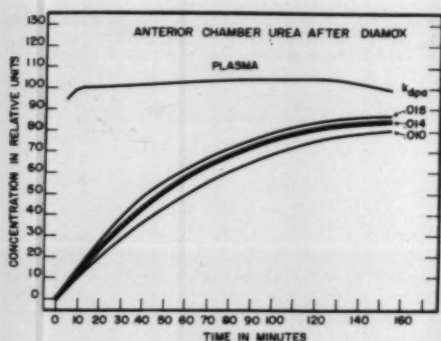


Fig. 8 (Kinsey, Reddy and Skrentny). Theoretical rate of accumulation of C^{14} -labeled urea in anterior chamber aqueous of Diamox-treated rabbits for three different assumed values of diffusion coefficient.

not only does urea diffuse into the eye relatively slowly ($k_{d,ph}$.036) but the amount entering by secretion ($k_{rh} \cdot C_a$) is also low because the concentration in the secreted fluid is only about 50 percent of that in plasma. Comparative rates of entrance by diffusion and secretion for urea, sodium and chloride in both chambers along with the concentration of these substances in the secreted fluid and their steady-state ratios, are summarized in Table 6. The table shows that sodium likewise diffuses slowly into the posterior chamber but the quantity entering by secretion is much higher than urea because of the higher concentration in the secreted fluid. Chloride, which like urea, appears to exist in the secreted fluid in a relatively low concentration has a rapid turnover in the posterior chamber because of the much higher diffusion rate. In the case of the anterior chamber urea has the lowest rate of diffusion.

It is interesting to observe the effect that diffusion rate has on steady-state ratios of substances in the aqueous. Although the quantity of urea and chloride entering the posterior chamber by secretion is almost

TABLE 4
EFFECT OF SYSTEMICALLY ADMINISTERED PITRESSIN ON THE TRANSPORT OF C^{14} UREA INTO THE AQUEOUS HUMORS

Time (min.)	Concentration Posterior Aqueous		Concentration Anterior Aqueous	
	Plasma		Plasma	
	Normal*	Pitressin Injected	Normal*	Pitressin Injected
	%	%	%	%
16	—	34	—	14
	—	35	—	15
	—	38	—	16
AVERAGE	33	36	16	15
31	—	30	—	23
	—	39	—	27
	—	41	—	31
AVERAGE	42	37	28	27

* From Figure 3.

TABLE 5
EFFECT OF INTRAVITREALLY ADMINISTERED PITRESSIN ON THE TRANSPORT OF
C¹⁴ UREA INTO THE AQUEOUS HUMORS

Time (min.)	Concentration Posterior Aqueous			Concentration Anterior Aqueous		
	Plasma			Plasma		
	Normal*	Pitressin Injected	Saline Injected	Normal*	Pitressin Injected	Saline Injected
	%	%	%	%	%	%
20	—	42	52	—	34	37
	—	38	45	—	26	33
	—	32	31	—	18	15
AVERAGE	35	37	43	20	26	28

* From Figure 3.

identical, the relatively more rapid rate of diffusion of chloride leads to a significantly higher steady-state, 89 percent compared with 72 percent for urea. The idea that diffusion rate is a prime factor in determining the steady-state ratio is further illustrated by the increase in steady-state ratio of urea in the posterior chamber after Diamox (85 percent vs. 72 percent), despite the reduction in the amount of urea entering by secretion.

COMMENTS

In calculating the concentration of urea in the secreted fluid the assumption has been made that the concentration is a constant linear function of its concentration in the plasma. The assumption introduces some error into the calculations, the magnitude of which is not apparent and will have to be

determined as further improvements in techniques may provide means for evaluating it experimentally.

Elevation of the steady-state ratio following administration of Diamox is not unique for urea. For example, Becker¹⁰ has shown that the steady-state ratio of ascorbic acid in aqueous of both posterior and anterior chambers is increased significantly by Diamox. He accounts for the elevated steady-state ratios on the grounds that while secretion of the acid is reduced by about a quarter, flow is depressed by at least one half, and generalized by stating that whether the steady-state ratio increases, decreases or remains the same depends upon whether water transport is suppressed more or less than the substance in question. Applying this explanation to urea, where it is assumed that Diamox sup-

TABLE 6
RATES OF FLOW AND DIFFUSION INTO POSTERIOR AND ANTERIOR CHAMBERS, CONCENTRATION IN THE
SECRETED FLUID AND STEADY-STATE RATIOS OF CONCENTRATION OF UREA,
NA AND CL IN RABBIT EYES

	Posterior Chamber				Anterior Chamber		
	Flow	Diff.	Conc. Sec. Fluid	$\frac{C_h}{C_p}$ St. St.	Flow	Diff.	$\frac{C_a}{C_p}$ St. St.
	$k_{fb} \text{ min.}^{-1}$	$k_{d,ph} \text{ min.}^{-1}$	$C_a \text{ Rel. Units}$	%	$k_{fa} \text{ min.}^{-1}$	$k_{d,pa} \text{ min.}^{-1}$	%
Urea normal	0.06	0.036	50	72	0.013	0.010	84
Urea Diamox-treated	0.03	0.072	36	85	0.0065	0.014	97
Na	0.06	0.030	98	97	0.013	0.013	97
Cl	0.06	0.15	47	89	0.013	0.018	94

presses water transport (flow) by half, turnover of urea in the posterior chamber is not suppressed at all but increases slightly, thereby resulting in a significant elevation of the steady-state ratio.

The observed increase in diffusion of urea across both the ciliary process and iris following administration of Diamox appears to be the first instance in which this drug has been shown to affect intraocular fluid dynamics other than by reducing flow. While one can only conjecture as to the possible mechanism by which diffusion rate is increased, the interesting electron microscope pictures of Holmberg²¹ come to mind. He showed that in the nonpigmented epithelium of the rabbit ciliary process Diamox leads to an enormous increase of small vesicles, the exact nature of which remains obscure. However, the probable alterations in the cell membranes suggest the possibility that increased diffusion may simply be the result of mechanical damage to the ciliary epithelial cells. In any case the present observations raise the interesting question of the extent to which diffusion and flow are independent variables—a problem for future experimentation.

SUMMARY

The rates of accumulation of urea in the

aqueous humors of the posterior and anterior chambers of the rabbit eye following parenteral administration of C¹⁴-labeled urea have been determined. From the observed rates, diffusion coefficients between plasma and posterior and anterior chambers and the concentration in the fluid secreted into the posterior chamber have been calculated.

Diamox administered parenterally was shown to increase the rate of accumulation of urea in the posterior and anterior chambers as well as the steady-state ratios in all of the ocular chambers. The rate of accumulation of urea was unaffected by either the systemic or intravitreal injection of pitressin.

Diamox was also shown to increase the rate of diffusion of urea across both the ciliary process and iris—an effect which is interpreted to be chiefly responsible for the increased rate of accumulation and steady-state ratios.

A mathematical method is described which makes it possible to take into account the diffusional contribution from the vitreous to the posterior chamber of any substance under steady-state conditions when failure to allow for such transport (as is the case for urea) would lead to serious error in computing transfer coefficients.

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THE EFFECT OF ACETAZOLAMIDE ON THE RESPONSE TO ANTERIOR CHAMBER PUNCTURE IN MAN*

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The effect of acetazolamide on aqueous dynamics in man has been studied principally by chemical analysis of the anterior aqueous, by observation of the appearance time of fluorescein in the anterior chamber, and by tonometry and tonography. The results of these tests indicate that acetazolamide causes a reduction of the prevailing rate of aqueous flow by an average amount of about 50 percent, and a corresponding lowering of the intraocular pressure.¹ Clinically acetazolamide has been used as a pressure-lowering agent in various forms and phases of glaucoma, and in a variety of other situations. Its use has been advocated particularly before, during, and after operations for cataract and

glaucoma, and for the treatment of delayed anterior chamber restoration after such operations. An essential step in these operations is the release of the anterior aqueous. It therefore seemed of interest to study the effect of acetazolamide upon the response of the human eye to the release of the anterior aqueous, that is, to the surgical procedure usually called anterior chamber puncture.

In studies of this kind on experimental animals Leopold, et al.² found that the administration of acetazolamide prior to paracentesis increased the time required for the restoration of its intraocular pressure and for the reformation of its anterior chamber. Appelmans and Michiels³ observed no difference in the rate of chamber reformation between acetazolamide-treated and untreated rabbits.

In man, to our knowledge such studies have not been reported.

* From the Department of Ophthalmology, University of Illinois, College of Medicine. Supported in part by a grant from the National Society for the Prevention of Blindness.

METHOD AND MATERIAL

The technique of anterior chamber puncture used in this study differs slightly from that previously described.⁴ Surface anesthesia is obtained by repeated instillations of ophthalmine. Fixation of the globe with two properly placed conjunctival fixation forceps is adequate for a consistent technique of aqueous aspiration. The puncture is made with 27-gauge stainless steel hypodermic needles mounted on chemically cleaned calibrated tuberculin syringes. Entry into the cornea is usually made through the temporal limbus below the horizontal meridian and at an angle of 30 degrees with a tangent laid through the point of entry. This results in an intracorneal track two to three mm. in length; only the tip of the needle enters the chamber. The aqueous is slowly aspirated until the iris around the needle tip comes in contact with the cornea. A sudden contraction of the pupil that is superimposed upon the gradual contraction paralleling the aspiration often marks the moment when the iris touches the cornea. At the same time, the operator may feel a definite resistance of the plunger to further withdrawal. Thus a very definite end-point is reached which limits and defines the fluid volume which can be aspirated by this technique. At this end-point, traces of fluid

may still be present in other parts of the chamber which are not in communication with the tip of the needle. To remove those traces the needle would have to be moved to other parts of the chamber which would increase the irritation of the iris and the injury to the cornea beyond the degree ordinarily entailed in anterior chamber punctures. The needle is therefore not carried to other parts of the chamber. The fluid volume obtained in this manner is considered to be an estimate of the volume of the anterior chamber (for the purpose of this study).

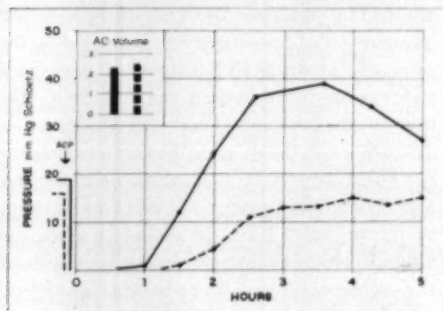
Tonometric readings with standardized Schiøtz tonometers and, when feasible, with two different weights are taken just before (T_1) immediately after (T_0) and from then on about every half hour after the puncture (T_1 , T_2 , T_3 , etc.). No consistent changes in ocular rigidity were observed during the procedures followed in this study. The restoration of the anterior chamber is observed photographically and the reaction in the chamber checked by biomicroscopy for a period of three to four hours.

The effect of acetazolamide upon the response to anterior chamber puncture was studied in four patients presenting different stages and degrees of open-angle (chronic simple) glaucoma (table 1). To establish a

TABLE 1
CLINICAL DATA

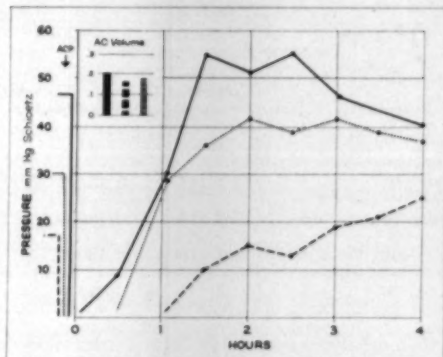
No.	Patient	Age	Eye	Corrected Visual Acuity	Field Loss	Glaucomatous Disc Changes	Pressure* Range (mm.Hg)
1	J. B. #4481, white male, incipient cataract	60	R	20/50	None	Borderline	25-30
			L	20/250	+	+	25-30
2	C. O'N. #191728, colored male	80	R	20/80	++	++	26-33
			L	20/80	+	+	24-33
3	L. McK. #70662, colored male	60	R	Nil	+++	+++	40-55
			L	20/15	None	None	25-35
4	C. C. #113311, colored male	46	R	Nil	+++	+++	37-65
			L	20/20	++	++	35-45

* Without treatment.



Graph 1 (Kronfeld and Freeman). Effect of acetazolamide on the response to anterior chamber puncture.

baseline, one puncture was performed after all forms of antiglaucomatous treatment had been discontinued for at least one week. The patient was then placed on acetazolamide, 250 mg., three times daily, and another puncture was performed on the second day of this treatment. In one patient (Case 3) the effect of this treatment was compared with that of topical administration of Carbachol. The course of the intraocular pressure after the anterior chamber punctures is shown in Graphs 1 to 4. Solid lines denote the pressure readings without antiglaucomatous treatment, while the broken lines refer to the measurements on acetazolamide therapy. The dotted line in Graph 2 describes the course of the



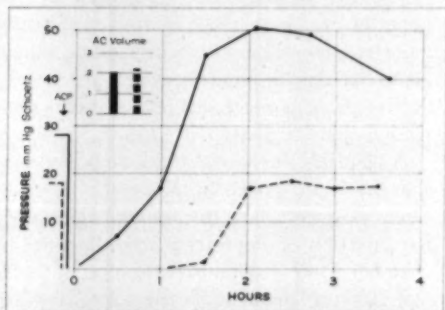
Graph 3 (Kronfeld and Freeman). Effect of acetazolamide on the response to anterior chamber puncture.

intraocular pressure after anterior chamber puncture under the effect of Carbachol.

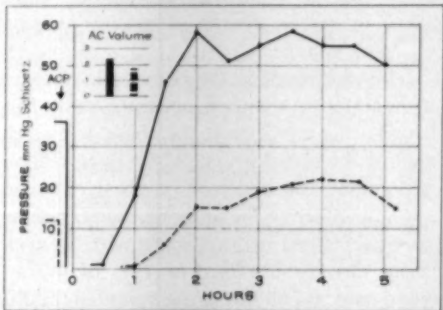
PRINCIPAL PHENOMENA ELICITED BY ANTERIOR CHAMBER PUNCTURE

The fundamental aspects of the response of the human eye to anterior chamber puncture are the restoration of the anterior chamber to its original volume and shape and the return of the intraocular pressure to its original level.

The restoration of the anterior chamber may be followed quantitatively by reaspiration of the chamber contents at different intervals after the first aspiration. A series of



Graph 2 (Kronfeld and Freeman). Effect of acetazolamide on the response to anterior chamber puncture.



Graph 4 (Kronfeld and Freeman). Effect of acetazolamide on the response to anterior chamber puncture.

TABLE 2
REFORMATION OF AQUEOUS AFTER ANTERIOR
CHAMBER PUNCTURE IN MAN

Interval (min.)	n	Volume of Chamber Contents at Second Puncture	
		Mean	Range
10	5	0.112	0.102-0.125
30	5	0.175	0.140-0.185
60	6	0.210	0.180-0.225
90	4	0.225	0.205-0.255

such measurements on 20 human control eyes with presumably normal aqueous dynamics and chamber volumes from 0.20 to 0.26 ml. is shown in Table 2. The rate at which the anterior chamber refills is fastest during the first few minutes after the initial puncture and declines thereafter as a negative exponential function of time. During the first 10 minutes aqueous is reformed at a rate greater than 10 μ l/minute, that is very much faster than normal. During the next 20 minutes this rate drops to an average of 3.5 μ l/minute which is within the normal range.

The rate of aqueous reformation also depends on the original chamber volume, the amount of fluid reformed being greater, per time unit or after the same length of time, in eyes with initially deeper chambers. This somewhat greater output, however, does not completely make up for the greater initial fluid loss so that the restoration of the anterior chamber to its original shape and depth takes longer in eyes with greater original chamber volume.⁵

The recordings of the intraocular pressure after anterior chamber puncture show four phases: the initial drop, the phase of restoration of the initial pressure, the hypertensive, and finally the hypotensive phase. The immediate effect of the anterior-chamber puncture performed in accordance with the technique already described on eyes of average build and in all the eyes reported in this paper was a drop in pressure to a level below the range of Schiötz tonometer. Other attempts to measure the actual pressure level

attained by complete emptying of the anterior chamber (T_0) have been of no avail. The results of intentionally incomplete punctures and various observations on eyes with unusually shallow chambers⁴ suggest that T_0 depends upon the relationship between chamber volume and total volume of the globe and upon the initial pressure. Greater uniformity of the pressure levels immediately after the anterior chamber puncture may be expected if extreme variants with regard to the original chamber volume and with regard to the initial pressure are excluded. The former requirement has been met by limiting this study to eyes with an anterior chamber volume between 0.15 and 0.25 ml. The second requirement could not be met because of the profound tension-lowering effect of the acetazolamide in some of the glaucomas.

The second phase in the alterations of the intraocular pressure elicited by anterior chamber puncture is the restoration of the intraocular pressure to its original level. Called the resoration time⁶ in previous publications this phase is conveniently measured in minutes and varies, in control eyes, from 70 to 140 minutes, again depending on the original chamber volume. The time required for return of the intraocular pressure to its original level is of approximately the same length or slightly longer than the time required for the restoration of the anterior chamber volume to its status quo.⁶

The restoration time is followed by the hypertensive phase which is characteristically more pronounced in eyes with chronic simple glaucoma than in control eyes.⁴ The hypertensive phase is succeeded by a greatly variable hypotensive phase.

A plausible interpretation of these pressure changes is suggested by Kleinert's observations on aqueous flow in episcleral veins after the injection of fluorescein into the anterior chamber.⁷ For distinct visualization of aqueous-carrying channels on the scleral surface filters are placed into the illuminating and observation system of the biomicroscope. By combining the injection of fluorescein with

the aspiration of a major portion of aqueous ("Minderdruckfuellung") conditions similar to those after anterior chamber puncture by the standard technique are created.

During the initial hypotony following the aspiration combined with the injection of fluorescein no aqueous-carrying channels can be seen in the episclera. At a fairly definite point during the reformation of aqueous and restoration of the intraocular pressure clear fluorescent channels become visible, exhibiting the phenomenon of flow at first intermittently and, a few minutes later, continuously. Kleinert has measured the intraocular pressure at which this continuous flow is resumed in aqueous veins (p_k). In normal eyes this pressure varies from about 6.0 to 12 mm. Hg and corresponds closely to the episcleral venous pressure. In eyes affected with chronic simple glaucoma p_k is reached during the phase designated as the restoration time. Up to the level of p_k one may assume that no appreciable bulk outflow occurs from the anterior chamber. Above the level of p_k continuous flow occurs and increases in magnitude until the eye, and particularly the glaucomatous eye, enters the hypertensive phase. At this time the visible aqueous flow slows down again and may come to an actual standstill. Visible flow is resumed as the hypertensive phase subsides and the intraocular pressure starts to drop back to the initial or a lower level. These observations of Kleinert's suggest that the mechanism of the hypertensive phase is that of an increase in resistance to aqueous outflow which is part of the reaction to the anterior chamber puncture.

The hypotensive phase following anterior chamber puncture, if of sufficient magnitude and duration to lend itself to analysis by tonography, has proved to be due to a reduction in the rate of aqueous production.

RESULTS

The effect of acetazolamide on the response to anterior chamber puncture is shown in Graphs 1 to 4. The response characteristics are also listed, together with the

tonographic data, in Table 3 where the figures in numerator position refer to the performance of the eye without any treatment and the figures in denominator position to the performance under the influence of acetazolamide. From this evidence the effect of the drug may be described as lengthening of the restoration time and diminution, if not elimination, of the hypertensive phase. In Cases 1 and 2, the drop in flow rate and intraocular pressure under the influence of the drug was of the magnitude that one would expect in eyes with chronic simple glaucoma and only slightly elevated intraocular pressure. The complete elimination of the hypertensive phase was impressive and unexpected since strong hypertensive reactions are a characteristic of eyes affected with chronic simple glaucoma even if the initial pressure is well within the normal range.⁴

In Cases 3 and 4, the drop in pressure under acetazolamide treatment was greater than usual and was associated, in Case 3, with a strikingly large drop in flow rate (from 1.96 to 0.40 $\mu\text{l}/\text{min.}$). Both patients had undergone one anterior-chamber puncture without any therapeutic agent a week before. The impression is created that the anterior-chamber puncture renders eyes with advanced chronic simple glaucoma more susceptible to the flow rate-lowering effect of acetazolamide. This possibility might be of practical clinical value and calls for further investigation.

The response to the second anterior puncture (the first one under acetazolamide) was typical in Patients 3 and 4, typical in the sense that the restoration time was lengthened and the hypertensive phase greatly reduced. Furthermore, a very marked hypotensive phase made its appearance after the anterior chamber puncture and persisted for about a week after discontinuation of the drug. This hypotensive phase proved to be due to a profound drop in flow rate which again may be a finding of practical clinical value. Needless to say the hypotony was not associated with any clinically detectable state of iritis, cyclitis or choroidal detachment.

TABLE 3
EFFECT OF ACETAZOLAMIDE ON AQUEOUS DYNAMICS
(Untreated/Treated)

Case No.	Tonography*			Anterior Chamber Puncture		
	P ₀	C	F	Initial Pressure	Restoration Time	Hypertensive Phase
1 Left	21	.21	2.31	19	108	++
	16	.19	1.20	16	>300	None
2 Right	27	.10	1.7	28	70	+++
	X	X	X	18	140	None
3 Right	38	.07	1.96	46	80	+++
	15	.08	0.40	17	170	+
4 Right	37	.08	2.16	36	80	+++
	23	.09	1.17	12	110	+

* Average of at least two measurements.
X = Not determined.

DISCUSSION

The prolonged restoration time and the marked hypotensive phase after anterior chamber puncture under the influence of acetazolamide fit in well with the current, well-founded concept that acetazolamide inhibits a segment of the secretory processes which are concerned with the elaboration of aqueous. Further studies with different drug dosages, different time relationships and on other forms of glaucoma may contribute toward a sharper definition of the acetazolamide-sensitive part of the secretory processes.

The mechanism whereby acetazolamide inhibits the hypertensive phase after anterior chamber puncture is not immediately apparent. In three of the four cases reported the hypertensive phase was reduced to a subnor-

mal intensity, which is encountered only in a very small percentage of control eyes ("eyes with slight reaction" [Strassmann^{8,9}]). To blame this very weak reaction just on a low flow rate does not seem like an adequate explanation since even a very slow flow should give rise to a substantial rise in pressure once the restoration time is over and the resistance to outflow increases as is suggested by Kleinert's observations. A possible explanation is suggested by considering the time course of the hypertensive phase in Cases 2, 3 and 4 and in cases reported earlier.⁴ The assumption that the typical increase in outflow resistance underlying the hypertensive phase occurs during and only during the second hour after the anterior chamber puncture would furnish an explanation since

at that time the acetazolamide-treated eye is still engaged in the process of restoring its anterior chamber and therefore relatively independent of the condition of its outflow channels.

The response to anterior-chamber puncture brings out the fundamental difference in pharmacologic action between the carbonic anhydrase inhibitors, on the one hand, and the cholinergic stimulants on the other (graph 3). Carbachol, a typical representative of the latter group, does not delay the restoration time and only slightly mitigates the hypertensive phase.

SUMMARY

The effect of acetazolamide on the response to anterior chamber puncture was studied in four patients presenting different stages of chronic simple glaucoma. In the usual dosage acetazolamide reduced the rate of reformation of aqueous, delayed the restoration of the anterior chamber and the return of the intraocular pressure to the initial level and reduced or eliminated the usual hypertensive reaction after anterior chamber puncture. Some of these effects may account for the clinical usefulness of the drug.

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EXAMINATION OF LENSES OF STEROID-TREATED RATS*

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Bilateral granular opacities at the posterior pole of the lens were observed and reported recently in 17 out of 47 patients with rheumatoid arthritis subjected to long-term treatment with high doses of steroids. These

changes did not occur in 19 patients with the same disease who were not treated with steroids.^{1,2} It was concluded that the lens changes most likely had resulted from the therapy. In the present work, the influence of chronically administered high doses of steroids on lens structures of the rat was investigated. The known morphology and morphogenesis of several forms of experimentally induced cataract in the rat made

* From the Ophthalmology Branch, National Institute of Neurological Diseases and Blindness, National Institutes of Health, Public Health Service, U.S. Department of Health, Education and Welfare.

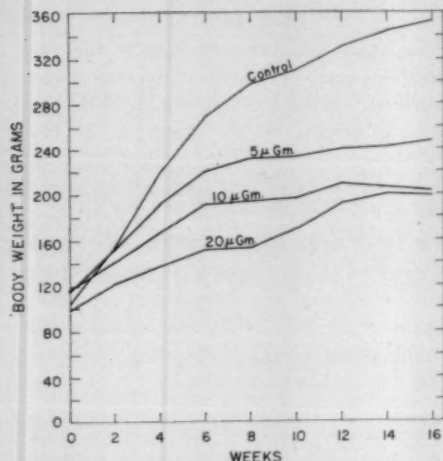


Fig. 1 (von Sallmann, Caravaggio, Collin and Weaver). Graph demonstrating that the most severely affected animals were those receiving the high dose of Decadron.

this species especially favorable for such a study.

METHODS

Thirty-five male rats of the Sprague-Dawley strain, five-weeks of age, and weighing 100-200 gm., were fed Purina laboratory chow ad libitum. For 16 weeks three animals of each litter of five received daily subcutaneous injections of Decadron (16 α -methyl-9 α -fluoro- Δ^1 -hydrocortisone), while the remaining two were injected with similar volumes of the solvent. Five, 10 or 20 μ g. per 100 gm. body weight were administered to the experimental animals of the individual litters. In addition, the dose of 20 μ g. per 100 gm. body weight was fed to five animals by stomach-tube. The material was prepared from a stock solution containing five mg. of Decadron in 25 ml. of 50-percent ethanol. Dilutions were made with an 0.9-percent solution of sodium chloride in such a way that, although the amount of steroid varied, the volume of injection did not exceed 0.8 ml.

Body weight and food consumption were recorded twice weekly. Fasting blood sugar

levels were determined in intervals of approximately three weeks according to the technique of Nelson and Somogyi.^{3,4} The blood samples were obtained by heart puncture.

Biomicroscopic examination of the eyes was carried out weekly and, in the last two months of treatment, on alternate weeks. When the experiments were terminated after 16 weeks the animals were killed by decapitation. The right eyes were embedded in celloidin for histologic examination and the left eyes were processed for cytologic studies of whole flat mounts of the lens epithelium with the Feulgen technique used in this laboratory. A few animals died at earlier periods at the occasion of withdrawal of blood from the heart. Their eyes were also studied systematically as described. Altogether 70 eyes were examined.

OBSERVATIONS

The animals receiving steroid treatment grew at a considerably slower rate than their littermate controls. The degree of growth inhibition varied even in the same dose group. The curves plotted in Figure 1, however, demonstrated that the most severely affected animals were those receiving the high dose of Decadron, 20 μ g./100 gm. At the 10- μ g. level, growth was not as markedly suppressed, while at the 5.0- μ g. level the inhibitory effect was mildest. The growth curve of the control animals closely resembled that recorded in normal untreated animals of this strain.

The blood sugar values obtained from the steroid-treated animals were in the range of the controls (table 1), except for a few instances in individual animals which had been treated for about two months. The blood-sugar levels in these cases showed a slight transient elevation.

On biomicroscopic examination, all lenses were found to be clear, or occasionally contained small congenital opacities in the lens nucleus.

Cytologic examination of Feulgen-stained

TABLE 1
BLOOD SUGAR LEVELS OF STEROID-TREATED AND CONTROL RATS

μg of Decadron per 100 gm. Body Weight	Weeks after Treatment Started				
	2½	4	6½	8	10
20	74 ± 13.1 (5)*	83 ± 18.4 (5)	88 ± 22.5 (4)	64 (1)	
10	79.5 ± 19 (9)	88 ± 18 (9)	79 ± 7 (9)	92 ± 34 (7)	89 ± 7 (3)
5	87 ± 24 (3)	84 ± 20 (3)	63 ± 2 (3)	86 ± 13 (3)	85 ± 6 (3)
Control	82 ± 24 (9)	89 ± 15 (12)	68 ± 12 (9)	75 ± 6 (7)	79 ± 6 (6)

* Numbers within parentheses indicate number of animals.

mounts of the lens epithelium did not disclose signs of cell degeneration. The mitotic counts tabulated in Table 2 indicated in some instances a moderate depression of cell division; but as a rule the values fell within the range of those observed in the control animals. The number of mitoses in the epithelium preparations of rats which died accidentally at an early phase of the experiment also did not differ from the average for that age group.

Histologic examination of the right eyes in the experimental and control groups likewise failed to show lesions of the epithelium, and signs of injury to the nuclei of the lens bow or the superficial cortical fibers. In view of the known histopathology of very early ophthalmoscopically invisible lens changes which are produced by various cataractogenic agents, great care was taken to study the architecture of the lens bow, the displacement of bow nuclei, and the subcapsular migration of equatorial cells toward the posterior or anterior pole of the lens. In all instances, the equatorial areas of experimental lenses was found to be normal and the arrangement of the bow nuclei was indistinguishable from that in control animals.

Similarly, the fibers of the lens cortex did not deviate from the normal. Such changes as hydropic swelling of fibers, homogenization of the fiber cytoplasm, or vacuole formation were consistently absent. Moreover,

the insertion of the fibers at the suture system did not differ from the normal anatomy. The morphology of the tissue elements at the posterior pole of the experimental animals and the control littermates were identical.

DISCUSSION

The clinical picture of the lens opacities which have been observed in steroid-treated patients does not resemble any experimentally induced cataracts of the rat. In this species, posterior cortical opacities are usually widely spread and do not exhibit the distinct granular pattern with interspersed vacuoles which characterize the lesion in the human. In contrast to this, the rabbit lens might develop a granular type of cataract following the exposure to ionizing radiations. These fine lesions are white dots in the slitlamp beam and black in transillumination. They are usually located around the posterior lens

TABLE 2
MITOSIS COUNTS IN LENS EPITHELIUM OF STEROID-TREATED AND CONTROL RATS*

μg of Decadron per 100 gm. body weight	Number of Animals	Average Counts
20	7	67 ± 25
10	7	73 ± 26
5	3	78 ± 16
Control	12	82 ± 21

* The counts of epithelial preparations obtained post mortem from rats which had died incidentally and those of incomplete mounts are omitted.

sutures and sometimes subcapsularly at the posterior polar region.

A detailed description of these opacities has been given by Cogan and Donaldson,⁵ and Cogan, Goff, and Graves.⁶ The authors showed that the white punctate opacities are caused by cells which have migrated from the equatorial zone of the epithelium to the posterior pole. Similar white dots, not localized at the area of the posterior pole, can be seen in the cortex of rats and mice lenses after exposure to ionizing radiations and recently have also been identified as displaced and swollen bow nuclei or migrated cells originating from the germinative zone of the epithelium.⁷

The lesions observed in steroid-treated patients are reminiscent of early radiation cataract in the human. It is known from experimental work that in these instances the cytopathology is not limited to the posterior cortex layer, but is preceded by cytologic changes of the germinative zone of the epithelium, of the bow nuclei, and the cytoplasm of the superficial lens fibers.

In the present work, such sites of early cell injury observed microscopically in several forms of experimental cataract were subjected to careful examinations, using histologic and cytologic techniques. By combining these methods and biomicroscopy, it is possible to study changes in cell division and cell degeneration of the epithelium, together with incipient lesions of the lens bow and the lens fibers. Since no signs of injury to the cell elements, or abnormalities of the normal architecture of the posterior pole were observed, it was concluded that chronic administration of high doses of steroid does not affect the rat lens adversely. These nega-

tive findings are another example of species specificities of cataractogenic agents. It will be necessary to extend similar studies to other species in order to contribute to the question of the pathogenesis of steroid-induced human lens opacities.

Retardation of body growth, paralleled by a diminished total body protein of cortisone-treated rats, has been reported by Hausberger and Hausberger.⁸ These investigators suggested that visible infections, particularly at the site of the injection, are responsible for the depression of weight gain which was most pronounced in rats with large cutaneous abscesses. Such infections were not observed in our series where the relative uniformity of the effect on growth and the dose dependency of the decreased weight gain did not support the concept that suppression of body growth in rats on high doses of steroids is brought about by complicating infections.

SUMMARY

1. Litters of Sprague-Dawley rats were treated for 16 weeks with daily subcutaneous injections of Decadron in doses of 5, 10, and 20 $\mu\text{g.}$ per 100 gm. body weight. In five animals, 20 $\mu\text{g.}$ per 100 gm. of the steroid were fed by stomach-tube.

2. The treatment resulted in all instances in retardation of body growth and, in a small number of animals, in a transient slight elevation of the blood sugar level.

3. The lenses of these animals were studied biomicroscopically, histologically and cytologically. They remained clear and light microscopic examination did not suggest an induced injurious effect on the cellular elements of the lens.

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GALACTOSEMIA CATARACT: A REVIEW*

REPORT OF A CASE

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Galactosemia is a relatively rare disease; only approximately 50 cases have been reported. Cataracts are present in about 75 percent of them. A review of the case reports that are available would seem to permit the drawing of certain conclusions and generalizations.¹⁻²⁷

As François²⁷ has pointed out, galactosemic cataract can make its appearance within the first few days or weeks of life. It is important to keep this possibility in mind when seeing what appears to be a congenital cataract. Cristine²⁹ has warned that in the presence of a "congenital" cataract, a galactosemia must be kept in mind, even if the cataract is the only noticeable clinical feature. He has been able to collect some cases in which the sole outstanding clinical symptom was cataract and where the diagnosis of galactosemia was possible only by the galactose tolerance test.

Galactosemia has been reported under the titles of galactosemia, galactosuria or galactose diabetes. Of these terms, galactosemia is the now generally accepted one.

Galactosemia is a hereditary disturbance of the carbohydrate metabolism in which the body is unable to metabolize galactose (lactose). When galactose is administered to the body it is normally hydrolysed by an enzyme

(lactase) in the intestine into its two components: glucose and galactose; these two components, due to a phosphorylation process, become absorbed and channelled into the liver by the portal circulation.²⁷ This conversion requires the presence of several enzymes and co-enzymes. It has been demonstrated that galactosemia is due to the lack of uridyl transferase.²⁶ It is the lens that in this disorder lacks the enzyme galactose-1-phosphate uridyl transferase.²⁸ The oxidative metabolism of the lens epithelium is markedly impaired. However, the exact mechanism of cataract development requires further investigation.

Working with the white rat, Hörmann³¹ believes that lactose and galactose inhibit carbohydrate catabolism. By the injection of co-carboxylase the effect of these two sugars is counteracted and the appearance of galactogenic cataracts is prevented. It is suggested that the latter may be due to a disturbance of the pyruvic acid-lactic acid equilibrium.

While Reuss¹ was the first to report the presence of sugar in infants most authorities feel that the first accepted case of galactosemia was reported by Göppert,² in 1917, in a child aged two years and five months. Two siblings of this child had died in early life, presenting icterus and enlarged livers. No mention was made of the eyes in this report. The essential clinical features of this disease are severe malnutrition, galactosuria, galacto-

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semia and hepatomegaly. Cataracts are present in a very high percentage especially if the disease has been present for some time. Long-standing cases may exhibit mental retardation. Untreated galactosemia is frequently fatal; however, on simply removing galactose from the diet, a dramatic clinical improvement occurs, with return of the liver to normal size, weight gain and termination of the galactosuria and the galactosemia. In some instances there is a regression of the cataracts.

The first authors to report the presence of lens changes in galactosemia were Mellinkoff and his co-workers⁸ who in September, 1945, reported a "sharp zone of demarcation in that the nucleus was more highly refractile; there were no actual opacities, however." They were also the first to report that the removal of milk from the patients' diet produced a complete disappearance of the lens changes. However, most authors feel that Bruck and Rapoport,⁹ who published their paper two months after that of Mellinkoff, were the first to report the presence of cataract in galactosemia and were the first to point out cataract formation as a complication of galactosemia.

It has been known for years that cataracts could be produced in rats by feeding them on galactose or lactose. This has been well summarized by McAuley.²²

In 1939, Gifford and Bellows³⁰ described the histologic changes present in the lenses of white rats fed on a diet containing 50-percent galactose but in which all known essential food factors were included. They found that the degeneration of the lens affected the young fibers near the equator, following the course of these fibers toward the anterior and posterior poles. They further found a layer of unaffected tissue next to the capsule which suggested that the young fibers continue to be laid down from the posterior cells of the capsule epithelium more rapidly than degeneration becomes apparent. Changes in the capsule and in the capsular epithelium, they felt, came on quite late. The nucleus and a

layer of cortex ensheathing it were apparently intact in all stages except when the cataract was in a mature state.

Animals which showed early cataractous changes and which were then fed on a normal diet showed ophthalmoscopically a complete disappearance of the opacities. Further examination, however, did reveal the remains of degenerative fibers just peripheral to the nucleus. These areas of degeneration had been compressed toward the center of the lens by a layer of newly formed, apparently normal fibers. Gifford and Bellows state that, in their observations, the nucleus was the last part to be affected.

CASE REPORT

Michael T. (U249384), aged four months, was admitted to the University of California Medical Center on April 25, 1956.

History. The mother stated that the child had been vomiting for three days; seemed to be irritable and listless and had not gained weight normally. At birth he weighed five pounds 14 ounces; at two months, he was eight and a half pounds and at the time of admission at four months, he weighed nine pounds. He was previously admitted to the Washoe Hospital at the age of six weeks for an acute upper respiratory condition which responded well to treatment. When discharged he was put on a diet of simlac and strained vegetables.

Family history. There were two siblings, a boy aged six years and a girl aged two years, both living and well. The balance of the family history was also negative.

Physical examination. The patient was a thin, pale, undersized child with deep-set eyes. He seemed irritable and listless and was passing frequent yellow-orange stools. The head circumference was 39 cm. and the anterior fontanel was open. The abdomen revealed an enlarged liver down to the umbilicus with sharp edges. The abdominal veins were prominent. Exclusive of the eyes, the balance of the physical examination was negative.

Laboratory findings. The two hour postprandial blood sugar was 220 mg. percent; the blood urea nitrogen 9.3; the albumin-globulin ratio 2.9/2.7 gm. percent. The electrolytes of sodium, potassium, chloride, phosphorus and the alkaline phosphates were normal. Urinalysis showed 3+ albumin; 3+ sugar; 1+ acetone and occasional granular and hyaline casts.

Diagnosis. Galactosemia.

Treatment. Child was placed on nutramigen diet with resultant gain in weight in one week and a marked improvement in his general condition. The child has been seen at four-month intervals since that time in the Pediatric and Metabolic Clinics and his progress has been satisfactory.

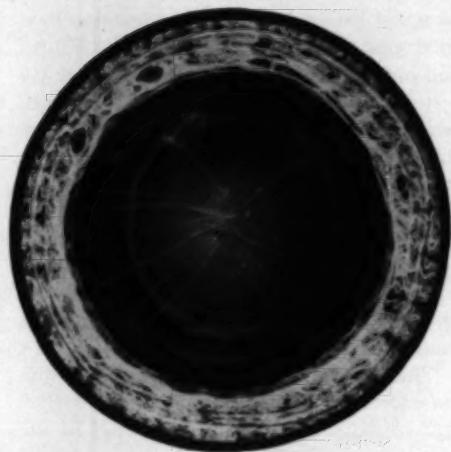


Fig. 1 (Cordes). Galactosemia cataract, right eye.

Ophthalmological examination. The patient was referred to the Department of Ophthalmology for consultation as soon as the diagnosis of galactosemia was made. When seen on May 1, 1956, examination showed a searching type of nystagmus without apparent fixation. The dilated pupil revealed bilateral zonular cataracts surrounding the fetal nucleus with fine punctate opacities in the periphery of the lens. The fundus of the right eye was grossly negative. The left fundus could not be visualized (fig.1).

He was not seen again until he returned to the Eye Clinic on March 6, 1957. The mother stated that in the interval, his general condition had improved markedly and that his searching nystagmus had disappeared but that she noticed that the left eye tended to turn out at times. It was also apparent that he had difficulty with his distance vision. Examination revealed no evidence of exotropia and the bilateral cataracts seemed unchanged except for the diminution of the peripheral punctate opacities.

The patient was again seen on April 30, 1958, with an intermittent exotropia of variable amounts. The lens opacities seemed about the same. A stereoscopic photograph was taken of the lens changes with the Donaldson camera. Atropine was suggested. The parents then moved to Mississippi and the child was not seen again until January, 1959.

The findings at this examination seemed the same. Atropine had not been used and it was again suggested as a possible aid to his vision.

He returned in December, 1959, with the cataracts appearing to be unaltered. There was a variable left exotropia of 35 to 45 prism diopters. He could see 20/60 objects at approximately three feet. The mother stated that he had no difficulty getting around. Atropine was continued.

He returned in February, 1960, with the same findings but the mother stated that the child asked

for the atropine drops now and she was certain that he saw better with them.

The child has been seen at intervals since that time, being seen last on August 3, 1960. The condition remains the same as judged from observation and a series of stereoscopic photographs.

It is felt that the child will not see well enough to carry on normally in school and now that the parents are in a location where this can be done, surgery is contemplated in the near future.

CATARACTS IN GALACTOSEMIA

Fifty cases of galactosemia reported in the literature were reviewed in regard to the presence of cataract in the cases reported. In four of the reports no mention was made of the eye examination. Eleven cases showed no evidence of lens changes and, in 35, cataracts were present.

In the 11 instances without lens changes, in the case reported by Mellinkoff and his co-workers, the disease was diagnosed at two months and the child was put on a proper diet immediately. No lens changes developed during the follow-up of this case. Bell and his group¹³ saw a child without lens changes who died on the eighth day due to hepatic changes. A sibling of this child was put on a galactose-free diet at birth and up to seven months had shown no evidence of developing cataracts.

Townsend's second case¹⁶ was put on diet at six weeks and at the end of eight years had shown no evidence of cataract formation. The third case, a sibling of Case 2, was put on a galactose-free diet prophylactically at birth and in a follow-up through 20 months, the lenses were clear. His fourth case was diagnosed at five months and, at the end of 23 months, there was still no evidence of cataract formation. This is the oldest child in the literature with untreated galactosemia who did not develop cataracts. DuShane and Hartman¹⁸ made no mention of the eyes in their report of a four and one-half-months-old child. In a personal communication to Patz,²⁰ however, they stated that careful examination showed no opacities.

In Wilson and Donnell's report of 12 cases,²⁴ there were four in which lens opaci-

ties did not develop. Case 8 was diagnosed at one month of age but had been on a lactose-free diet from birth. One and a half years after the diagnosis was made the media were still clear. Case 9, with a family history of galactosemia, was put on a lactose-free diet at birth. Eight months later, there was no sign of developing cataracts. The 10th case was diagnosed at three months of age with the media clear at that time. When seen five months later, there were no changes. In Case 12, the diagnosis was made at five and one-half years but the child had been on a lactose-free diet from birth because of a brother's history of galactosemia. There was no evidence of cataract formation. The galactose-tolerance test was abnormal at five and one-half years.

From these reports, it would seem that if a child with galactosemia is put on a lactose-free diet before lens changes appear their formation can be prevented. It is noteworthy that this was also true in a case that had undiagnosed galactosemia up to five years of age.

As François²⁷ has stated cataracts have been found to exist in at least 75 percent of all cases of galactosemia. A survey shows a good many variations in the lens changes as reported. The cataracts are always bilateral.

According to François²⁷ the early stages are characterized by enhancement of nuclear or perinuclear refractive power which has been described a number of times as giving the appearance of a drop of oil in the crystalline center.

Of the 35 cataracts reported, there were seven in which the lens changes were described as resembling a drop of oil, or giving the appearance of a refractile ring. In Patz's third case,²⁰ in a three-weeks-old infant, there was this central refractile annular zone at the surface of the fetal nucleus. Johnson¹⁹ reported a similar picture in his first case, that of a three-weeks-old infant. The patient reported by Bruck and Rapoport⁹ was seven weeks of age, while Turnbull's patient²³ was seven weeks of age. The patient in Patz's second case was eight weeks of age. Gold-

stein and Ennis¹¹ reported the condition in a child aged two and one-half months. Turnbull's second case revealed this drop of oil picture at two and one-half years. It is interesting that in this case the mother stated that this child had independently limited her milk intake, preferring to drink "apricot nectar." Thus we see that the patients in whom there was enhancement of nuclear or perinuclear refractive power were all under three months of age, with the exception of Turnbull's second case that was on an "independently limited" milk intake.

There were seven instances in which the cataract is described as zonular, or lamellar. The description varies a good deal. In the case reported by Falls and his co-workers¹⁷ the cataract is described as "a sharply outlined zonular area of increased density of an opalescent nebular nature just beneath the capsule in both lenses. In addition, it was evident that the nuclear areas were likewise opalescent in character." Reiter and Laskey²¹ describe the lamellar cataracts as round, thin and well demarcated. The zonular opacities varied from these thin, sharply demarcated cataracts to the one described in this case report.

There were eight cases in which the opacities were described as nuclear. These varied from faint opacities to François²⁷ description of diffuse, homogenous cataracts of the fetal nucleus, and Norman and Fashena's⁷ dense nuclear cataract. There were three cases merely listed as disciform cataracts that probably also belong in this category. Goldbloom and Brickman's¹⁰ first case with "dense central opacities" in all probability should be included in this category. In one case, the cataracts were described as "nuclear and peripheral." Goldbloom and Brickman¹⁰ reported that in their second case there were bilateral pinpoint opacities. Johnson¹⁹ stated that his third case showed tiny punctate opacities scattered throughout all layers of the lens and grouped together in condensed masses to form the lamellar portion of the cataracts.

Wilson and Donnell²⁴ reported two of

their cases as having posterior cortical opacities and, in McAuley's first case,²² the opacity was described as "postcapsular in one eye and centrally placed in the other."

In McAuley's second case²² the changes were described ophthalmoscopically as "faint striate opacities that were seen to radiate from the clear central area of both lenses; these appear to be situated anteriorly and simulated a wrinkling in the lens capsule."

Dustlike opacities were observed in two of the cases reported by Wilson and Donnell²⁴. Fleury and Berger³² described the opacities as saucerlike, anteriorly and posteriorly.

Thus, while there is a good deal of variation in the opacities that have been described in the lenses in galactosemia, it would seem that in the very early stage the typical change is an enhancement of nuclear or perinuclear refractive power producing the "drop of oil" appearance. Later, while there are variations most of the cases develop zonular or nuclear cataracts. If the disease is not treated the cataracts have a tendency to progress fairly rapidly and may become intumescent.

It has been generally assumed that if the diagnosis of galactosemic cataract is made before the patient is over three months of age, resorption of the lens opacities will take place if treatment is instituted. Johnson¹⁹ stated "It may not be stated dogmatically but one can certainly say that removal of milk from the diet before the third month of age is imperative for prevention of irreversible lens changes." Reiter and Laskey,²¹ in 1952, said that it can be stated roughly that diagnosis and vigorous treatment of the disease before two or three months of age may be expected to result in complete resorption of any lenticular opacities present. However, in 1958 Wilson and Donnell²⁴ reported 12 cases and stated that no regression of cataracts was observed in any case, even when appropriate dietary treatment was instituted immediately following diagnosis. Their cases included four patients who were three months of age or less. In the case reports studied here, there were 16 patients three months or less in age when lens

changes were discovered. Of these, only seven showed clearing.

Of the cases that regressed, Bruck and Rapoport⁹ reported a seven-weeks-old infant in whom the opacities disappeared. Goldstein and Ennis¹¹ reported similar results in a two and one-half-months-old child; however, five years later Patz²⁰ examined the patient on the slitlamp and found fine punctate opacities on the posterior surface of the fetal nucleus. Reiter and Lasky's patient²¹ was seven weeks of age, while McAuley's²² first patient was four weeks of age and the second patient was six weeks of age. Turnbull's²³ first patient was seven weeks of age and at the follow-up, he stated that the "cataracts had almost completely disappeared." In François's²⁷ first case, that of a six-weeks-old child, the opacities had disappeared at the age of three months. In Enns' patient, aged six weeks,¹⁴ there was partial clearing.

It will be noted that in all but one case in those whom clearing took place, the age was less than two months. In this one case, as already noted, Patz found some opacities on the posterior surface of the fetal nucleus. Thus, it would seem that the chances of clearing are poor unless the infant is under two months of age.

Of the 50 cases of galactosemia, there were 11 cases that showed no evidence of lens changes at the time of diagnosis and did not develop opacities under observation after the diet had been instituted. Bell's first case,¹³ Townsend, Mason and Strong's¹⁶ second case and Wilson and Donnell's²⁴ eighth and 12th cases were all put on a lactose-free diet from birth because of the history of galactosemia in the family and in none of them did cataracts develop while under observation, one case being followed for five and one-half years. The age of the remainder varied from four days to four and one-half months in DuShane's case.¹⁸ DuShane does not mention this in his paper but in a personal communication to Patz he stated that the lenses revealed no opacities on follow-up.

Some opacities which were described as cleared when seen ophthalmoscopically, on

slitlamp examination showed some changes. For example, in the case reported by Goldstein and Ennis¹¹ it was stated that after two months there was no residual but when Patz²⁰ examined the patient with the slitlamp five years later, he found fine, punctate, glistening opacities on the posterior surface of the fetal nucleus. Enns¹⁴ found nuclear or perinuclear haziness at seven months. Patz's²⁰ second patient at a 38-month follow-up showed several glistening punctate or fine irregular opacities and a few minute opacities in the subcapsular cortex. These opacities were not visible with the ophthalmoscope. This suggests that the cases that showed "complete resorption" ophthalmoscopically did not clear completely. This would be in keeping with Gifford and Bellows'³⁰ observation already mentioned. They found in rats that the early cases put on a normal diet revealed complete disappearance of the opacities ophthalmoscopically but that histologic examination revealed the remains of degenerated fibers just peripheral to the nucleus.

In some of the less advanced cases, there was slight improvement without complete absorption.^{6, 10, 12, 19} In the remainder of the cases, the opacities did not change or went on to further or complete opacification that required surgery.

If treatment is not instituted, the cataracts that are present usually progress dramatically and rapidly become mature. From the few reports available, the surgery of these cataracts would seem to offer no particular difficulty if the usual precautions used in congenital cataract surgery are observed. In the case reported by Norman and Fashena,⁷ the resultant vision was 20/80 in the right eye and 20/40 in the left, while in Mason and Turner's case⁶ the resultant vision was 20/30 in each eye.

Galactosemia depends upon an hereditary factor which Falls and his co-workers¹⁷ feel may well be an innate error of metabolism most likely exhibiting a simple autosomal recessive mode of inheritance. François²⁷ has pointed out that there have been numerous

observations (40 percent) that show familial incidence of the disease in children of siblings, without the siblings themselves having shown evidence of the disease.

The presence of consanguinity has been noted by Fanconi,⁵ in 1933, and by Flury and Berger,³² in 1955. Falls¹⁷ also mentions consanguinity and states that the presence of consanguinity and the multiple occurrence of the disease in siblings gives weight to the hypothesis that the disease exhibits a simple autosomal recessive mode of inheritance.

Holzel and Komrower in 1955³³ and Holzel, Komrower and Schwarz,³⁴ in 1957, demonstrated galactose tolerance in parents of five galactosemia infants. In one case the test was abnormal in both parents; in another case, it was abnormal in only one parent. They conclude that the abnormal galactosemic curve represents the heterozygote stage and that the disease represents the homozygote stage.

SUMMARY AND CONCLUSIONS

A case of galactosemia seen in a four-months-old boy is presented. The ophthalmologic examination revealed bilateral zonular cataracts with some fine punctate opacities in the periphery of the lens. Following the removal of lactose from the child's diet, there appeared to be some clearing of the opacities so that the child no longer had a searching type of nystagmus. In the last three and one-half years that the child has been under observation, the cataracts appear to be stationary as seen on the slitlamp and from observations of stereoscopic pictures taken with the Donaldson camera.

A review of the 50 case histories of galactosemia that were available would seem to warrant certain conclusions.

1. Of the 50 cases, no mention was made of an eye examination in four instances. Eleven patients gave no evidence of lens changes and in 35 instances, cataracts were present. The condition was bilateral.

2. The youngest patients to be reported were three weeks of age, which stresses the

importance of keeping galactosemia in mind when seeing what appears to be a congenital cataract.

3. In 11 cases where no lens changes were present at the diagnosis of galactosemia, the institution of the proper diet prevented cataract formation.

4. A review of the cases with lens changes would seem to show that the earliest changes are an increased refractive power about the fetal nucleus giving the appearance of a drop of oil. This is usually followed by the development of either zonular or nuclear cataracts. In addition, some faint striate opacities in the anterior cortex, dustlike opacities, and saucerlike opacities have been described.

5. It has been stated that, if the diagnosis is made at the age of three months or earlier, regression will take place. Of the 16 patients reviewed, who were three months or less of

age at the time treatment was instituted, only seven showed regression. Except for one patient, aged two and one-half months, the others were all under two months of age. This would seem to indicate that the prognosis for regression is good only in those cases in which treatment is started before the child is two months of age.

6. Slitlamp examination in some instances with ophthalmoscopically complete resorption revealed some fine opacities. This agrees with the findings in experimental galactosemia cataracts in animals.

7. If treatment is not instituted, the cataracts that are present usually progress rapidly and become mature.

8. Surgery in these cases seems to offer no difficulty if the usual precautions used in congenital cataract surgery are observed.

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SURGERY FOR EXOTROPIA: FUSIONAL ABILITY AND CHOICE OF PROCEDURE*

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It has been my good fortune to have served with Francis Heed Adler in the preparation of three symposia on strabismus.¹⁻³ In each he made important contributions by relating basic physiology of binocular vision to strabismus. In this tribute to Dr. Adler, it therefore seems appropriate for me to present some studies of altered physiology in a strabismus problem. I have found that certain sensory factors, related to fusional ability, influence the results of my surgery for comitant exotropia. In my hands at least, choice of operative procedure also affects the results. These studies have altered my opinions concerning the choice of procedure and the amount of surgery for individual cases.

In 1953, it was the consensus of the panel on comitant strabismus of the American Academy of Ophthalmology and Otolaryngology¹ that:

Symmetrical procedures which safeguard normal motility should be given preference, particularly in younger children. However, the monocular recession-resection approach may be satisfactory especially in monocular strabismus

and in older patients in whom there is no prospect of regaining normal binocular cooperation.

As a member of this panel, I concurred in this opinion; however, my viewpoint has been changed by two critical reviews which I have made of the results of surgery for exotropia.

The first review, presented in March, 1955, to the Oregon Academy of Ophthalmology, was a 10-year survey of surgery performed for exotropia by residents of the University of Oregon Medical School, and by several faculty members in private hospitals. In all, 220 consecutive case records were reviewed. The choice of procedure generally was in agreement with the policy statement presented by the American Academy panel in 1953; that is, lateral rectus recessions generally were the primary procedures for alternating strabismus. Lateral rectus recessions combined with medial rectus resections were performed for monocular exotropia, and alternating exotropia with gross convergence insufficiency. Many of the records were inadequate for critical analysis of the results

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TABLE 1
FIVE-YEAR RESULTS OF VARIOUS OPERATIONS IN
220 CONSECUTIVE CASES OF EXOTROPIA

<i>Unilateral lateral rectus recession</i> Additional surgery recommended or performed in 36 out of 46 patients
<i>Bilateral lateral rectus recessions</i> Additional surgery recommended or performed in 44 out of 108 patients
<i>Unilateral recession-resection</i> Additional surgery recommended or advised in 11 out of 66 patients

of surgery, but they did provide enough controversial information to justify a better controlled study.

Comparisons of the preoperative and postoperative measurements were made but there were so many individual variations that results obtained by the various types and amount of surgery could not be averaged and directly compared. However, some conclusions could be drawn by determining the number of cases requiring further surgery either because of symptoms or poor cosmetic results. In nearly one half of 108 patients who had had bilateral lateral rectus recessions of five mm. or more, further surgery, usually medial rectus resection, was either advocated or actually performed within five years. Also, within the same five-year period, additional surgery was advised or actually performed on 36 of 46 patients who had had unilateral lateral rectus recessions as the primary procedure. In accordance with the observations of others, the results of lateral rectus recessions were best in those patients who had had a close near-point of convergence preoperatively but, even then, they were less consistent and less enduring than the corrections obtained by recession-resection. Further surgery was advocated, or actually performed, in only 11 out of 66 patients, five years after a unilateral recession-resection operation. The over-all data, summarized in Table 1, indicated that in exotropia, the reduction in the basic deviation obtained by lateral rectus recession was more apt to be enduring if a medial rectus resection was per-

formed on the same eye at the same time. This seemed to be true whether the patient had a monocular or an alternating exotropia.

In the first survey, there was one group of cases which merited special attention—patients who preoperatively demonstrated good fusional abilities and normal retinal correspondence. In this group, it did not seem to matter which operation was used providing that enough reduction in the deviation was obtained to make possible a normal type of binocular single vision under ordinary visual conditions. Then the basic deviation generally remained stable over a period of years. Stated otherwise, a normal fusional mechanism had a marked stabilizing effect.

The patients with normal correspondence and good fusional potentialities were noteworthy for another reason. Overcorrections were rare; but when they occurred, they produced disturbing symptoms, notably diplopia. An overcorrection requiring surgery was necessary in one of the cases operated on my service, but three other patients were seen with disabling symptoms of overcorrection from bilateral lateral rectus recessions performed elsewhere. Two of the three had had two or more operations directed toward correcting their postoperative esotropia; both had become incomitant. Preoperative evaluation of the sensory status in exotropia, therefore, has a considerable clinical significance, if only to recognize those patients with good fusional potentialities who are cured if the deviation is significantly reduced or eliminated, but who have serious problems if they are overcorrected.

Here, then, was case data which merited further investigation first because it was in conflict with the predominant opinion which favored symmetrical lateral rectus recession for alternating exotropia with good convergence; and second, because in the literature relatively little attention had been paid to the preoperative sensory state of these patients. Therefore, in 1955, I began a more critical study limited to patients examined by me and either operated by me or under my direct



Fig. 1 (Swan). Narrowed left palpebral fissure resulting from excessive medial rectus resection combined with lateral rectus recession.

supervision. The primary purpose of the second study was to compare the results of symmetrical lateral rectus recession versus recession-resection in patients with comparable sensory status and comparable deviation. The surgical techniques used in the second series of cases have been described in previous publications.^{4,5}

In the second series, no recessions of less than five mm. or greater than eight mm. were performed for the following reasons. In the cases operated early in the first survey, I found that lateral rectus recessions of less than five mm. were relatively ineffective, whereas recession of more than eight mm. often limited abduction and sometimes caused diplopia or cosmetic defect in lateral gaze. Also, I learned to limit the magnitude of medial rectus resections. There are references in the literature of resections of as much as 10 mm. of the medial rectus, that is, about one fourth of the total length of the muscle of the eye in the primary position. I found that resections of more than six mm. often led to a permanent narrowing of the palpebral fissure (fig. 1), as well as a limitation of abduction. In the second case series, resections were generally four to five mm. A noticeable narrowing of the palpebral fissure, although often present immediately after surgery, was not a lasting complication.

In the second review completed in 1960, over 200 consecutive cases were studied including some cases from the first series, but it was necessary to exclude a considerable number of patients. Excluded were those cases whose deviations and sensory status had not been accurately determined preoper-

atively; this eliminated children under three and one-half years of age. Also eliminated were cases which had had previous surgery for exotropia performed at other institutions or had a second operation within a few months. Incomitant exotropia and cases with either a considerable vertical component or a marked difference in the deviation in the upper and lower fields of gaze also were excluded. This reduced the series to 114 cases which were studied as follows.

Results of surgery were judged primarily on the basis of change in the basic deviation. Basic deviation is defined as the relative position of the visual axes when there is no stimulus to fusion, refractive errors are corrected, and the patient is fixating a distant object with his dominant or usually fixating eye. In all cases capable of stable central fixation, the basic deviation was determined by using the alternate cover test. In patients incapable of accurate alternate fixation, measurements were made of displacement of the corneal reflection on the deviating eye. All measurements were made with the patient wearing the full correction (as determined by cycloplegic refraction) and fixating a point of light 20 feet away on a blank wall. Nearly all patients were photographed before and after surgery.

Fusional potentialities were determined both by ophthalmologists working under ordinary room conditions and utilizing prisms, red-green, and polaroid filters, and by orthoptic technicians utilizing the major amblyoscope, after-image, and anaglyphic tests. An important observation was that intermittent exotropia was not a single clinical entity. Some patients who seemingly had normal binocular alignment at reading distances were found to lack simultaneous bifoveal perception and to have only peripheral fusion. In many of these cases, retinal correspondence was variable, seeming to be abnormal when the visual axes were divergent and approximately normal when they were aligned. On the basis of their sensory status there are, therefore, two groups of intermit-

TABLE 2
CLASSIFICATION OF COMITANT EXOTROPIA
ON SENSORY BASIS

A. Alternating	
1. Intermittent	
a. Normal correspondence with good fusional ability	
b. Variable correspondence and poor fusional ability	
2. Constant with anomalous correspondence	
B. Monocular	
1. Consecutive to esotropia	
a. Spontaneous	
b. Postoperative	
2. Secondary to sensory obstacles to fusion	
a. Impaired vision	
b. Aniseikonia	

tent exotropia. One with good and the other with poor fusional potentialities. Judged on the basis of sensory findings, there was still another type of alternating exotropia, constant exotropia with anomalous retinal correspondence. Monocular exotropia was divided into those cases which shifted from esotropia to exotropia either spontaneously or following surgery. Table 2 shows the simple five-group classification which was used for this survey. There were only a few cases which did not fit into one of the classifications.

The largest group of patients had intermittent exotropia with normal retinal correspondence and good fusional potentialities. The clinical features of this group are shown in Figure 2. Unilateral lateral rectus recessions of from five to as much as eight mm. were performed as the primary procedures in 15 cases, all operated prior to completion of the survey in 1955. Most were preschool children who had relatively small basic deviations (25 prism diopters or less), excellent convergence ability and 10 diopters or less of exophoria for near. The results, two years after surgery, are plotted in Figure 3. There were no overcorrections but satisfactory functional results were obtained in only six cases. These six were converted from intermittent exotropia to asymptomatic exophoria by reduction of the basic deviation to 12 prism diopters or less. Here, again, the stabilizing effect of a normal type of fusional



Fig. 2 (Swan). Intermittent exotropia with normal correspondence. Often familial. Generally good convergence. Normal type binocular single vision when fixating near objects (above). Basic exotropia manifest in day-dreaming or staring into distance (below).

mechanism was evident. Further surgery was recommended, or actually performed, on the remaining nine cases within five years of the first operation because none of these patients had had enough reduction in their basic deviation to maintain comfortable and comitant binocular single vision.

More consistent results were obtained when bilateral lateral rectus recessions were the primary procedure. Only 10 cases were operated before this technique was discontinued in 1955. All had normal retinal correspondence, good fusional potentialities and good convergence ability. The results are

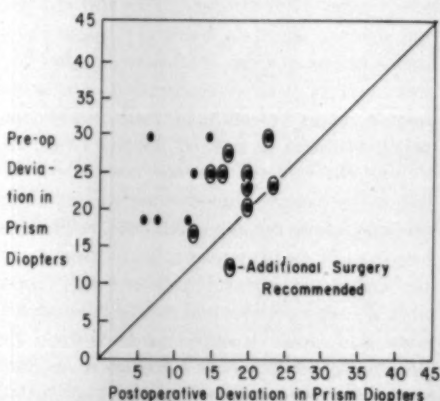


Fig. 3 (Swan). Basic deviation two years after unilateral lateral rectus recession in 15 cases of intermittent exotropia with good fusional ability.

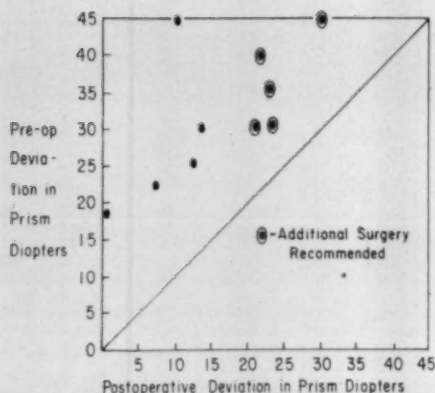


Fig. 4 (Swan). Basic deviation two years after bilateral lateral rectus recession in 10 cases of intermittent exotropia with good fusional ability.

shown in Figure 4. With one exception, the basic deviation was 22 prism diopters or more preoperatively. Reduction in this deviation to 12 prism diopters or less was obtained and comfortable binocular single vision was maintained in one half of the cases for at least three years after surgery. One of these cases was slightly overcorrected (esophoria three diopters), but all have been asymptomatic. The other five cases all had some improvement from surgery, but retained a basic deviation of 20 diopters of exotropia two or more years after surgery. This did not permit them to maintain binocular single vision under ordinary room conditions, so that further surgery was recommended. Unilateral medial rectus resection of four to five mm. was performed in four of the five cases. Although the interval between operations was two to five years, the outcome was good. In all four cases the deviation was reduced to less than 10 to 12 diopters, permitting a normal and stable type of binocular single vision.

In 20 cases with normal retinal correspondence and good fusional potentialities, the primary procedure was a five to seven mm. lateral rectus recession combined with a four to five mm. resection. In 19 out of the 20 cases, the deviation was reduced to less than

five diopters and maintained for follow-up periods of from 18 months to six years (fig. 5). Comfortable binocular single vision was restored in 18 out of the 19 cases. The 19th case was overcorrected but this patient, a five-year-old girl at the time of the surgery, has been comfortable wearing her full hypermetropic correction of two diopters with three diopters of base-out prism incorporated in her glasses. Her basic deviation two years after surgery is six to seven diopters of esophoria but is slightly less in near vision. Without glasses, this patient has constant diplopia in distant vision. It is hoped that her eso deviation will lessen as she grows older. The 20th case was the only one in this series requiring a second operative procedure. This patient had a preoperative deviation of 40 prism diopters, unusually large for intermittent exotropia with good fusional potentialities. This was reduced to 20 prism diopters by the unilateral recession-resection operation. The patient was able to overcome this deviation by fusional convergence and by accommodative effort (two diopters of uncorrected hypermetropia) but was uncomfortable. The deviation was eliminated by contralateral recession-resection performed two years after the first operation.

In summary, lasting good results were ob-

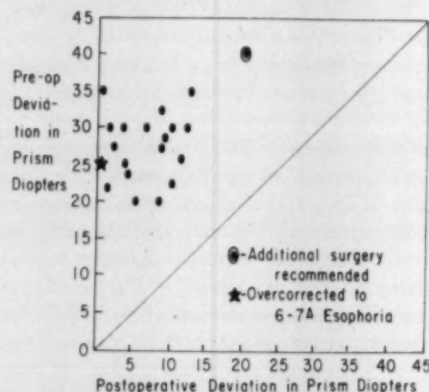


Fig. 5 (Swan). Basic deviation two years after unilateral recession-resection in 20 cases of intermittent exotropia with good fusional ability.

tained in this group of patients with normal correspondence and good fusional potentialities providing that the basic deviation was reduced to 10 to 12 diopters or less. There were exceptions but this amount of exophoria seemed to be the average minimal deviation which would permit the patient to maintain comfortable binocular single vision at all times under ordinary visual conditions. This goal was achieved much more consistently by unilateral recession-resection than when only lateral rectus recessions were performed. The stabilizing effect of good fusional movements again was quite evident in this group. In patients converted from intermittent exotropia to constant exophoria, the basic deviation remained relatively stable, whereas in those cases where the surgery was inadequate and intermittent exotropia persisted, the basic deviation tended to increase.

The next group seemed to have intermittent exotropia but really had only poor fusional ability and variable or normal correspondence. The clinical features of this group are described in Figure 6. Although the exotropia appeared intermittent in these cases, it actually was constant in distant vision and only gross peripheral fusion could be demonstrated in near vision. Critical studies with small targets revealed that bifoveal perception was lacking and that good alignment in near vision was maintained primarily by accommodative effort. Unilateral lateral rectus recession was performed as the primary procedure in six cases with relatively small deviations. All were operated prior to 1955. Further surgery was performed in five of the six within three years after the first operation. In two of these cases, the basic deviation was the same two years after the lateral rectus recession as it has been preoperatively. Eight patients had wide bilateral lateral rectus recessions performed as the primary procedure. Some reduction was obtained in the deviation in all eight cases, but further surgery (unilateral medial rectus resection) was required within three years on four of the eight cases. Satisfactory cosmetic



Fig. 6 (Swan). Intermittent exotropia with variable correspondence and poor fusional ability. Often familial. Deviation manifest early but relatively asymptomatic. Eyes well aligned in near vision (above). Constant exotropia for distant vision (below).

results were obtained by bilateral lateral rectus recession in only three cases (fig. 7). Although the basic deviation was reduced to 10 prism diopters in all three, only one developed bifoveal perception and stereopsis. A number of other cases also had intensive postoperative orthoptics but this patient was the only one with variable retinal correspondence before surgery who developed a normal type of binocular single vision following surgery. In this young man, the basic deviation was two to three diopters of exophoria 10 years after the bilateral lateral rectus re-

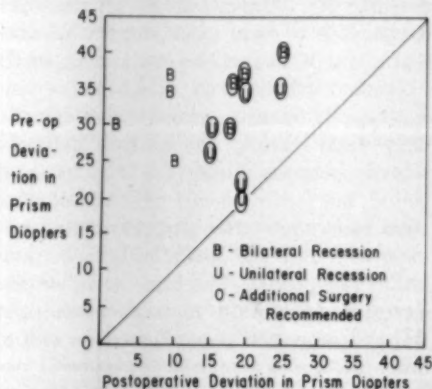


Fig. 7 (Swan). Basic deviation two years after lateral rectus recession in 14 cases of intermittent exotropia with variable correspondence and poor fusional ability.

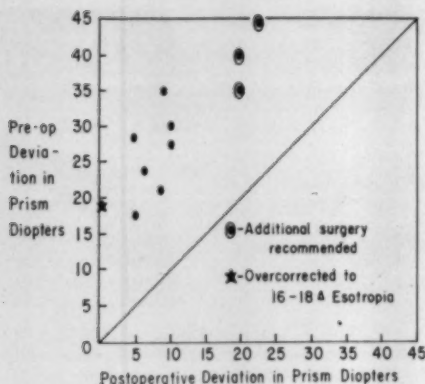


Fig. 8 (Swan). Basic deviation two years after unilateral recession-resection in 11 cases of intermittent exotropia with variable correspondence and poor fusional ability.

cession as compared to a preoperative deviation of 30 prism diopters. During the 10-year interval, the refractive error of this patient shifted from one diopter of hypermetropia to seven diopters of myopia, and his interpupillary distance widened from 54 to 65 mm., but his basic deviation remained constant.

Unilateral recession-resection was undertaken as the primary procedure in 11 cases of intermittent exotropia with poor fusional potentialities. Measurements of the basic deviation two years after surgery revealed that it was 10 diopters or less in eight of the 11 cases, and one had established a normal type of binocular single vision (fig. 8). Only three cases of the 11 had to have a second operation during this first two-year period, but measurements of the basic deviation four years after surgery in the eight cases with only one operation revealed quite a different picture. The basic deviation had increased significantly in four of the eight. Further surgery was performed on two of these four cases, primarily for cosmetic reasons. Here, again, the results of recession-resection appeared to be both more consistent and more lasting than lateral rectus recessions; however, in the absence of the sta-

bilizing effect of a normal type of binocular single vision, the deviation increased over a period of years in a significant number of these cases.

In this group of intermittent exotropia cases with poor fusional potentialities, one patient was grossly overcorrected. This was a child who had 2.5 diopters of hypermetropia and 22 to 24 diopters of basic exotropia. Preoperatively she had an excellent near-point of convergence. A unilateral recession-resection was performed. An overcorrection of eight to 10 diopters became evident within two weeks after surgery. It was reduced slightly by prescribing the girl's full hypermetropic correction (two diopters), but two years after surgery she still has 16 to 18 diopters esotropia for distance and near, wearing her glasses. This girl has not had further surgery because she is relatively asymptomatic and the esotropia is inconspicuous because of a wide angle Kappa. Her only symptom has been occasional diplopia. In her case, lack of normal binocular perception has been a blessing. It is hoped that with growth and development of her facial structure she will spontaneously lose some of the esotropia.

Seventeen cases of constant alternating exotropia were operated. The clinical features of this group are shown in Figure 9. These cases were found to differ from the

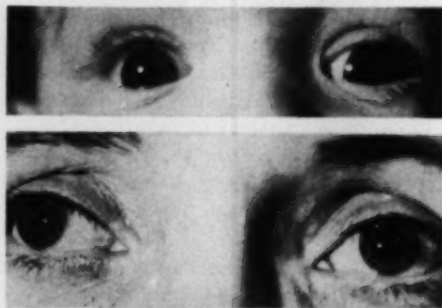


Fig. 9 (Swan). Constant alternating exotropia. Often familial. Deviation manifest in infancy (above). Large deviation which increases during life and is often associated with hypertropia (below). Correspondence abnormal. No fusional ability. Treatment primarily cosmetic.

intermittent group with poor fusional ability in several important respects. First this group demonstrated relatively little convergence with accommodative effort. Second, the basic deviation generally was larger than in the intermittent group and was noted at an earlier age. Third, retinal correspondence was anomalous by all tests.

Bilateral lateral rectus recession was performed as the primary procedure in only five patients with constant alternating exotropia. Four of the five had to have further surgery within two years. In recent years, on my services, only unilateral recession-resection has been performed for constant alternating exotropia. It was the primary procedure in 11 patients. One year after surgery reduction in the basic deviation was significantly greater than in the cases operated with bilateral recession (fig. 10). A more striking difference in results was evident when the postoperative deviations at fixation distances of 25 to 50 cm. were compared. Some improvement in convergence generally was achieved with medial rectus resection. This gave the patients who had recession-resection superior cosmetic results as compared to those who had only lateral rectus recessions.

Although the surgical results were adequate and orthoptic training was used postoperatively in many cases of alternating constant exotropia, correspondence remained anomalous and suppression persisted in all 17 cases. The stabilizing effects of normal fusion therefore were lacking. Measurements four to six years after the initial recession-resection indicated that the basic deviation had increased from three to as much as 10 prism diopters in all 17 cases of constant exotropia. In fact, a second recession-resection (on the opposite eye) was performed, or recommended, in four patients.

The final two groups surveyed had monocular exotropia. There were 11 cases of consecutive exotropia and 29 cases of monocular exotropia associated with sensory obstacles of fusion, such as, unilateral cataract and high anisometropia. Most of these pa-

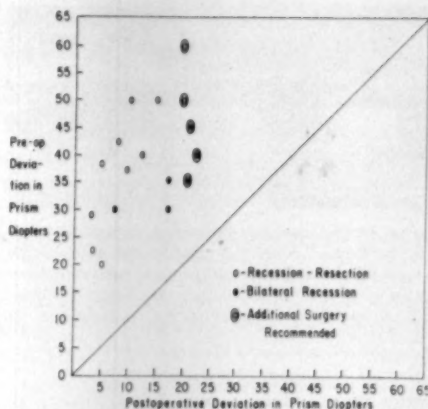


Fig. 10 (Swan). Basic deviation one year after surgery in 17 cases of constant alternating exotropia.

tients who had not had previous surgery had recession-resection of the deviating eye as the primary procedure so that no significant comparison could be made between recession versus recession-resection operations. Four to six mm. medial rectus resections were combined with recessions of the lateral rectus muscle up to eight mm. Only one overcorrection was obtained. The results were generally good one to two years after surgery but, in the majority of cases, the deviation had increased when measured four to five years after surgery. In some of those cases recession-resection was performed on the opposite eye before an adequate correction could be obtained. This is preferable to such radical surgery on one eye that the patient has a narrowed palpebral fissure and incomitant rotations (fig. 11).

In 69 patients with various types of exotropia, a medial rectus resection was performed one or more years after lateral rectus recession on the same eye. An attempt was made to compare the reduction in deviation to that obtained by recession-resection performed concurrently. Statistically significant data could not be obtained; however, some narrowing of the palpebral fissure was noted in nearly half of those cases in which medial



Fig. 11 (Swan). Enophthalmos, narrowed palpebral fissure and restricted rotation due to excessive surgery for monocular exotropia. The surgeon reported a 10-mm. medial rectus recession combined with an eight-mm. lateral rectus recession on the left.

rectus resection was performed a year or more after lateral rectus recession. The most logical explanation is that some contracture of a recessed muscle takes place if its antagonist is not simultaneously shortened or advanced.

In these two surveys of exotropia, case data were obtained on patients operated on as early as 1945, but it has been quite evident that additional long-range studies will be necessary before final conclusions can be drawn. For example, it was not possible in this study to determine with certainty the influence of the time of operation relative to the patient's age, nor was enough case data available to determine with certainty the influence of changing interpupillary distance and refractive errors in growing children. Also, no patients were studied who had medial rectus resections as the primary procedure.

There were some other factors considered in this study which were not reported, such as near-point of convergence, preoperative orthoptic training, degree of amblyopia, accommodative ability, and the wearing of corrective lenses. These and other factors will be considered in a subsequent report, but none were found to alter the validity of the data presented.

SUMMARY AND CONCLUSIONS

A survey of the results of surgery in 220 consecutive cases of exotropia was made by me in 1955. This survey indicated that in

patients with normal correspondence and good fusional abilities, functional cures could be obtained by either recessions or recession-resections providing that the deviation was reduced to an amount permitting binocular single vision at all times. This goal was achieved more consistently with moderate unilateral recession-resection than with lateral rectus recession. Overcorrection in this group of cases was found to produce distressing symptoms. If a normal type of binocular single vision did not develop postoperatively, the results from unilateral recession-resection were much more consistent and enduring than those obtained by a comparable degree of bilateral lateral rectus recessions. Unilateral lateral rectus recessions seldom were found to give an adequate amount of permanent correction.

The above survey prompted the faculty of the University of Oregon Medical School to consider changing from symmetrical lateral rectus recession to moderate monocular recession-resection as the primary procedure in all types of comitant exotropia. A second survey was made of 114 cases of comitant exotropia with particular attention to pre- and postoperative sensory status of the patient. On the basis of their sensory status, cases of alternating exotropia could be divided into three distinct groups: Intermittent exotropia with normal correspondence and good fusional potentialities; intermittent exotropia with variable correspondence and poor fusional ability; and constant exotropia with anomalous correspondence. Monocular comitant exotropia was divided into the cases secondary to sensory obstacles to vision, such as amblyopia and exotropia consecutive to esotropia.

Again it was found that intermittent exotropia with good fusional ability could be cured by reducing the basic deviation to establish an exophoria of 10 to 12 prism diopters or less; however, this goal was achieved more consistently by moderate unilateral recession-resection than with lateral rectus recessions.

In intermittent exotropia with poor fusional ability and in alternating constant exotropia, a normal type of binocular single vision seldom developed after surgery, even with intensive orthoptics. The stabilizing effect of fusional vergences was not present and most cases re-examined four to five years after surgery were found to have an increase in the deviation as compared to two years postoperatively. In these two groups, unilateral recession-resection gave much more consistent and enduring effects than lateral rectus recessions alone. The few overcorrections obtained in these two groups were well tolerated. More drastic surgery is indicated as compared to intermittent exotropia with good fusional ability.

In monocular exotropia, an effort was

made to confine the surgery to the deviating eye, but gross incomitance and alteration of the palpebral fissures was avoided by limiting medial rectus resections to four to six mm. and recession to seven to eight mm. Additional surgery on the usually fixing eye was found preferable to creating these disfiguring defects of excessive surgery on the deviating eye.

These data should not be interpreted as indicating that lateral rectus recessions are improper procedures for exotropia, but rather that results of operation can be made more consistent and enduring by concurrent medial rectus resection. This seems particularly important in cases lacking the stabilizing effects of normal fusional mechanisms.

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RETINAL PERFORATION DURING STRABISMUS SURGERY*

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The mechanics of muscle surgery are not unduly difficult and surgical complications are few. Most texts stress the problem of insufficient or excessive correction of a given strabismus case, rather than physical complications. Though the incidence of operative and postoperative difficulties is low, the variety of potential complications is extensive. One complication that has received virtually no scrutiny, however, is retinal hole formation occurring during muscle surgery.

A case of retinal tear formation occurring during recession of the inferior oblique

muscle was recently brought to our attention in a patient who was referred to us after muscle surgery elsewhere. It was not known whether to treat this tear, nor was it clear from the literature what risk there was of retinal detachment.

Consequently, a detailed examination of strabismus patients was undertaken, and immediate postoperative indirect ophthalmoscopy performed. In a rather short period of time, utilizing the private and ward patients of several hospitals, 16 patients were found who had unequivocal, surgically caused retinal tears about the sites of extraocular muscle manipulation. It soon became clear that a characteristically appearing tear is

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Fig. 1 (McLean, Galin and Baras). Appearance of the retinal perforation immediately following surgery.

caused, with apparently no retinal detachment resulting.

It is the purpose of this communication to report on this complication of strabismus surgery, describe its appearance, and comment on the prognosis.

MATERIALS AND METHODS

Patients were examined within the first 24 hours of strabismus surgery, and at regular intervals thereafter when retinal hole formation was found. When possible, detailed drawings of the fundus were made. At other times only sketches could be drawn, as examination time was, of necessity, quite limited.

RESULTS

A rather consistent sequence of events occurs following the induction of needle track retinal tears in young, healthy eyes, regardless of whether the needle is removed or even if the suture lies within the vitreous cavity. Initially, hemorrhage covers the perforation site (fig. 1). Some of the hemorrhage may break through into the vitreous cavity but, in the main, it remains confined to the choroid and retina. In a matter of a day or two, bare sclera is visible, usually surrounded by residual hemorrhage and light pigmentation. The area appears as if choroid

and retina were scooped out, leaving bare sclera behind. Our follow-up is not sufficiently long to determine the degree of pigmentation induced but it appears to be only slight (fig. 2).

We have come across several strabismus patients with this characteristic lesion, who have made uneventful recoveries from surgery performed several years prior to noting this finding. Here, too, the lesion appears identical.

DISCUSSION

It is well known that retinal tears are the forerunners of retinal detachments. This is true for both idiopathic detachments and traumatic detachments. However, more and more emphasis has been placed in recent years on the role of the vitreous in detachment production.

It is a not uncommon experience of detachment surgeons to perforate the retina during surgery. This event may occur at the time of fluid drainage or with the use of perforating instruments. If the induced hole occurs in detached retina and choroidal-retinal adhesions are not created about the hole, failure is likely.

In the normal eye, however, the mild trauma induced by perforation with a short needle is well tolerated. Probably hemor-

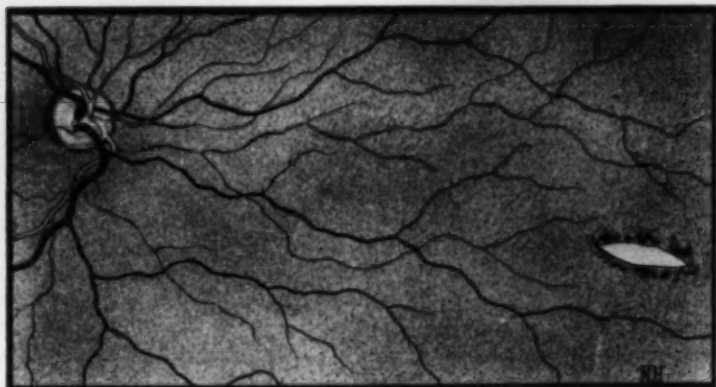


Fig. 2 (McLean, Galin and Baras). Appearance of the retinal perforation several weeks postoperatively. (Note the sparse pigmentation)

rhage seals the site until fibrous adhesions form. The vitreous change is negligible and consequently traction does not result. Certainly, one would think that any large-sized perforation would incur the risk of detachment.

It has not yet been possible to assess the frequency of this event. However, the ease with which this series was accumulated would indicate that retinal perforation during strabismus surgery is not rare.

The shape of needles used in strabismus surgery would seem to be important in this complication. The recent enthusiasm for "inverted" cutting needles may have been responsible for most of the complications noted here. It is possible that complete choroidal or retinal perforation did not always occur, but rather that the sharp leading convex edge deep in the sclera caused the tear by tissue stress and distortion. The theory of needle design is not a primary purpose of this communication but it would seem a reasonable conclusion that convex edges of needles used in muscle operations should not be sharp. If the surgeon always maintains pressure on his needle in the exact direction of the needle

curve and does not go too deep, these complications should not take place. However, if he tends to direct any force toward a sharp leading convex edge, the possibility of unrecognized and undesirable deeper cutting is obvious. The remedy lies in proper needle manipulation. An added safeguard would be use of a needle which is not sharp on the convex curve.

The first two cases in this series were treated with light coagulation and fared well. No other case received therapy, and in no case did detachment occur. One might infer, therefore, that no therapy is indicated.

SUMMARY

The complication of surgically induced retinal tear formation occurring during strabismus surgery is described. Though uncommon, this problem does not appear rare. No therapy seems warranted as retinal detachment does not occur. A characteristic-appearing retinal scar results. Proper selection and manipulation of needles should eliminate this complication.

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MODERN CONCEPTS OF THE ETIOLOGY OF UVEITIS*

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It is the purpose of this address to outline in simplified form the concepts now generally held on the etiology of endogenous uveitis, to trace their historical development, and to summarize briefly the basic evidence and recently developed knowledge which support them. In the limited time available at this Pan-American Congress only the highlights can be presented. Details are discussed and references will be given in a more lengthy communication soon to appear.

It is generally conceded that uveitis as a whole can be divided into two separate, etiologically distinct disease entities. In their early and uncomplicated forms, these two types of uveal inflammation have characteristic clinical and histologic pictures. Occasionally these two basic types of inflammation may merge into one another and when this occurs, the resulting uveitis is usually alluded to as a "mixed type."

The first basic type of uveitis is caused by an actual invasion of the uveal tissues by the causative pathogen. This pathogen is usually in living form although dead organisms or inert foreign substances may occasionally cause a similar reaction. The pathogens thus far identified in the uveal tissues are a variety of nonpyogenic organisms, protozoa, fungi, helminths, and so forth. On account of the ocular clinical symptomatology, the histologic picture, the frequent association of this type of uveitis with a group of systemic diseases known as the infectious granulomas, in 1941 the term "granulomatous" was suggested to describe this form of uveal inflammation.

The second basic type is believed caused by a sterile insult to the uvea. Theoretically

this insult may be a physical one, may be due to the action of toxins or irritants, or may result from a hypersensitivity reaction. However, there is little evidence to support either of the first two possibilities, and with few exceptions, this form of uveitis is believed to be the expression of an antigen-antibody reaction in the uveal tissues. The clinical picture is compatible with such an allergic insult, and the histologic picture is chiefly that of nonspecific inflammation. The term "nongranulomatous" was suggested to describe this form of uveitis.

"Mixed uveitis" is the term suggested to describe a uveal inflammation which, at one time or another, shows the clinical and histologic characteristics of both the two basic types. The most frequent cause of such a hybrid picture is a sensitization of the uveal tissues to the specific protein of a pathogen which primarily causes a granulomatous uveitis. A reaction between such sensitized tissues and any residual antigen would result in an allergic, nongranulomatous inflammation, superimposed on a basic granulomatous process. Other, less frequent causes, will be mentioned later in this lecture.

The terms "granulomatous" and "nongranulomatous" are not perfect and are undoubtedly open to criticism. However, they appear definitely superior and more descriptive of the etiologic differences than any others before or since suggested. They have been widely adopted in the last two decades, and are now firmly ingrained in the literature, and to attempt to supplant or change them now would be a source of endless confusion.

HISTORICAL DEVELOPMENT OF THE CONCEPTS OF GRANULOMATOUS AND NON- GRANULOMATOUS UVEITIS

For almost a century, ophthalmologists have recognized the two main clinical varie-

* From the Wilmer Ophthalmological Institute of the Johns Hopkins Hospital and University. Address of one of the guests-of-honor, VI Pan-American Congress of Ophthalmology, Caracas, Venezuela, February, 1960.

ties of uveitis, and have also noted that they might occasionally merge into one another. This clinical differentiation was made with little or no knowledge of the underlying pathology, or of different etiologies. For want of any other better names these two varieties of uveitis were usually termed "serous" and "plastic." There was, however, considerable confusion over the exact symptomatologies of these two entities. In general, the term "serous" was applied to a long, drawn-out, chronic type of uveitis without exudation in the anterior chamber, with manifest keratic precipitates, slow-forming posterior synechias, and gradually progressing organic damage to the eye. The term "plastic," on the other hand, was employed to describe an acute form of uveitis, usually self-limited in its course, but often recurrent, with a predilection for the anterior uvea, often with fibrinous exudation in the anterior chamber, and a tendency to the rapid formation of fibrinous posterior synechias.

Many thoughtful ophthalmologists refused to accept these terms and, in 1897, Norris and Oliver protested against this nomenclature. They emphasized that occasionally one type might merge into the other and stated that uveitis should be classified on an etiologic basis. They then proposed such a classification, one which was remarkably farsighted when the state of medical knowledge at that time is considered. In 1905, Fuchs said that the term "serous" was an unfortunate one and had no place in ophthalmologic writing. Thereafter, with the development of bacteriology and the dawn of immunology, these terms gradually faded from the literature and are rarely encountered after the second decade of the 20th century.

As advances were made in bacteriology, in immunology, and in physiologic chemistry, ophthalmologists sought to apply this new knowledge to the study of the etiology of uveitis. In the pre-Wassermann days, it was generally believed that the most frequent causes of uveitis were either a toxemia or syphilis. Thus, the popular forms of treat-

ment were pilocarpine sweats and mercurial inunctions, eliminative and antisypilitic therapy. When it was later shown that the protein-split products were highly toxic, there arose the idea that auto-intoxication might be an important cause of uveitis. This was believed to result from the absorption of toxic products formed in the gastro-intestinal tract. This idea soon became one of the fetishes of the day. High colonic irrigations thereupon became somewhat fashionable! However, when it was experimentally demonstrated that practically a lethal parenteral dose of these various protein degeneration products was required to produce even the slightest ciliary irritation, this "alimentary cult" began to lose caste. Similarly, with the introduction of the Wassermann reaction and the exact serologic diagnosis of syphilis, it was gradually realized that, at least among the Caucasian race, syphilis was an infrequent cause of uveitis. Ophthalmologists were therefore forced to seek elsewhere for explanations of the two forms of uveitis.

About this same time, German ophthalmologists were stressing the fact that many cases of uveitis, especially those of the so-called "serous" type, occurred in patients with an old systemic tuberculosis, or in individuals who were tuberculin hypersensitive. It was further pointed out that the clinical picture of these eyes, and the small amount of histologic material available from them, were both compatible with the pathology of tuberculosis. Thus the idea grew that, except for the few cases due to syphilis and occasionally to leprosy, all cases of chronic generalized uveitis were secondary to a tuberculous infection.

From 1912 to 1916, Billings introduced the theory of focal infection. This assumed that bacteria from a chronic systemic focus of infection migrated by way of the blood stream or lymph to more remote portions of the human body where they set up metastatic secondary foci—in the joints, in the appendix, in the eye, and so forth. This theory immediately gave physicians an explanation

for a variety of disorders for which previously they could find no cause. To ophthalmologists it offered a new method of treating uveitis. Under this theory, the obvious treatment was to remove the primary focus whence the infection had arisen. Thereupon there ensued a surgical holocaust—the wholesale removal of teeth, tonsils, and operations of the sinuses, gallbladder—all with the idea of removing the cause of the uveitis. The great majority of patients so treated made this sacrifice all in vain.

While this doctrine of focal infection was highly popular with many clinicians, it was equally unpopular with bacteriologists and pathologists, who pointed out that there was no evidence of this assumed bacterial metastasis and that the same organisms could not be cultured from the so-called primary and secondary foci. Furthermore, when the aqueous aspirated from eyes with acute iridocyclitis was cultured it was found, almost without exception, that the cultures were sterile.

It was noted, however, that occasional patients with acute iridocyclitis showed a most dramatic improvement after eradication of a systemic focus of infection. If the iridocyclitis in these patients was not due to direct bacterial metastasis from the primary focus to the eye, what was the relationship between the ocular inflammation and the systemic focus of infection? It was first suggested that in these cases the iridocyclitis might be due to bacterial toxins diffusing out from the focus of infection. However, it was soon proven that the bacteria commonly found in these foci did not produce exotoxins, and that any endotoxins which could be extracted from them were relatively weak and without action on the ocular tissues.

Beginning about 1908, first in Europe and later in America, a number of investigators began to study hypersensitive reactions in the eye. It was soon demonstrated that an inflammatory reaction, which had all the clinical characteristics of acute iridocyclitis in the human, could be produced in the eyes

of experimental animals by sensitization and later challenge with the specific antigen. In the earlier experiments, either the sensitizing or the challenging injection of the antigen was made directly into the eye. However, in 1938, MacLean produced this ocular reaction in rabbits with the bacterial type of hypersensitivity, by the systemic injection of both the sensitizing and challenging dose of the antigen. In these animals the only ocular traumatism involved was an anterior chamber puncture and drainage of the primary aqueous prior to the systemic injection of the challenging dose.

As a result of these clinical, bacteriologic, and experimental studies, it was suggested that acute iridocyclitis in man was usually a sterile reaction. Thereafter, the idea slowly crystallized that any relation such as uveal inflammation might have to a systemic focus of infection was dependent upon a sensitization of the uveal tissues to bacterial proteins from the systemic focus and the later challenge by the same specific antigen.

These two concepts—that the chronic, so-called serous, type of uveitis was due to an actual infection of the uvea, and that the acute, so-called plastic, type was usually a hypersensitivity phenomenon—became the generally accepted ideas on the etiology of uveitis during the 1925-1940 period. How greatly these concepts dominated ophthalmologic thinking at that time is well illustrated by the first (1941) report from the Wilmer Institute on the etiology of uveitis.

In this report the histories of 562 patients with uveitis, studied in the Wilmer Institute from 1925 to 1939, were reviewed and analyzed. Of this total, 248 had what was believed to be the infectious form of the disease. The remaining 214 cases were believed to represent inflammations resulting from sterile insults to the uveal tissues.

A "positive" or "presumptive" etiologic diagnosis was assigned to each of these 562 cases. The positive diagnoses were based on what at that time was considered adequate

and justifiable evidence. The presumptive diagnoses were based on admittedly tenuous evidence and were in fact little more than a guess. However, there was no significant difference in the percentage incidence attributed to different etiologic factors in these two classes of diagnoses. In the over-all total, of the 248 cases of granulomatous uveitis, 80 percent were ascribed to tuberculosis, 17 percent to syphilis, and three percent to scattering causes. Of the 214 cases of nongranulomatous uveitis, 69 percent were believed related to foci of infection through some undetermined hypersensitivity mechanism, 12 percent were attributed to gonococcal infections, 16 percent to some associated nongranulomatous systemic disease, and three percent to various scattering causes.

Prior to 1941, these concepts of the division of uveitis into two basic types, and the recognition that at times both types of inflammation might be present in the same eye, were supported by little more than clinical observation, suggestive experimental findings, and inductive reasoning. During the last two decades, however, further clinical observations, experimental investigations, and histologic studies have been presented, all of which support the original hypotheses. This evidence, as concerns granulomatous, nongranulomatous, and the mixed type of uveitis, may be summarized as follows:

GRANULOMATOUS UVEITIS

The investigations on granulomatous uveitis have, in the main, been channeled along the following lines:

A. The search for hitherto unrecognized, or only vaguely suspected, pathogens—bacteria, protozoa, fungi, helminths, viruses, and so forth—which may be actual causes of uveitis.

B. A study of the immunologic reactions produced in the host by pathogenic agents believed responsible for granulomatous uveitis.

C. The use of newer diagnostic procedures

—therapeutic trial tests, immunologic reactions, and so forth—as aids in establishing an etiologic diagnosis.

In the time available for this address, it is impossible to enumerate here the many significant contributions which have been made along these paths. As concerns the etiology of granulomatous uveitis, suffice to say that the most important contributions lie in the first category. These are the demonstration that sarcoidosis, brucellosis, acquired toxoplasmosis, infections with hook-worm larvae and probably benign histoplasmosis must now be considered as highly important causes. The evidence for these etiologies may be briefly summarized as follows:

SARCOIDOSIS-BRUCELLOSIS

In the first Wilmer report it was stated that undoubtedly many cases of uveitis due to sarcoidosis and chronic brucellosis had been erroneously ascribed to tuberculosis. In the second (1944) study, a special search was made for evidences of these two diseases. This study was based on 200 consecutive cases of uveitis of which 157 could be classified as granulomatous, and 43 as nongranulomatous. Somewhat more rigid diagnostic criteria were used, and cases in which the evidence did not appear sufficient to justify even a presumptive diagnosis were listed as of "undetermined etiology." Eleven percent of the 200 cases were so classified.

In the 157 cases of granulomatous uveitis, there were 15 histologically proven cases of sarcoidosis, an incidence of 10 percent. This incidence is somewhat higher than would ordinarily be expected for the reason that at the time this study was made (1941-43) sarcoidosis was a subject of special investigation in the Medical Clinic of the Johns Hopkins Hospital. There were also 15 cases of proven chronic brucellosis in these 157 patients, and in these patients no other cause could be found to explain the uveitis. This incidence of 10 percent is also higher than was encountered in later studies, the reason

being that at that time there was discovered, just beyond the Baltimore city limits, what amounted to almost an open focus for the dissemination of a *Brucella* infection, and an abnormally large number of cases of chronic brucellosis were observed during this period. With the eradication of this focus, the number of these cases of the systemic disease and likewise of *Brucella* uveitis, fell off sharply.

Despite the fact that the percentage incidence of both sarcoidosis and chronic brucellosis as etiologic factors in granulomatous uveitis may have been unduly heightened by the factors just mentioned, this study conclusively demonstrated that both of these systemic granulomatous diseases must be recognized as definite causes of granulomatous uveitis, and they must be considered and sought for in any etiologic study.

ACQUIRED TOXOPLASMOSIS

The most dramatic advance of recent years in the etiology of adult granulomatous uveitis was the discovery, made by Wilder in 1952, of the *Toxoplasma gondii* in the necrotic chorioretinal lesions of 52 adult eyes which had previously been erroneously diagnosed as atypical tuberculosis but in which tubercle bacilli could not be found. It had been known for many years that toxoplasmosis was a frequent cause of a focal congenital chorioretinitis and that the parasite was present in the ocular lesions. However, despite a number of suggestive reports to the contrary, it was generally believed that the eyes were not involved in the frequent asymptomatic, adult systemic infection. The discovery of the parasite by Wilder in the chorioretinal lesions of adults stimulated a great flood of clinical, serologic, histologic, and experimental investigations. It is now generally recognized that not only is toxoplasmosis a proven cause of adult endogenous granulomatous uveitis, but that it is one of the most important causes. The percentage incidence ascribed to toxoplasmosis as the etiologic factor in adult granulomatous uveitis varies in

different studies, but in many clinics the figure now runs as high as 30 percent or more.

FUNGI—HISTOPLASMA CAPSULATUM

It had been known for years that various pathogenic fungi were occasional intraocular invaders. These pathogens produced the clinical picture of a semipurulent endophthalmitis or of multiple small abscesses. Histologically, these eyes showed chronic inflammatory foci surrounded by a granulomatous reaction of epithelioid and giant cells, in some instances suggestive of the histologic picture of sympathetic ophthalmia. Intraocular infections with these pathogenic fungi were rare and up to 1949 (Cogan) only 11 such cases had been reported in the literature. Since then there have been only scattered reports of additional cases.

Despite the rarity of proven intraocular infections with the virulent fungi, it had been repeatedly suggested that ocular invasion by other relatively nonpathogenic fungi, notably the *Histoplasma capsulatum*, might be a highly important cause of granulomatous uveitis. This suggestion was based on the fact that since 1943 it had been known that benign, asymptomatic histoplasmosis was a widely prevalent infection, in some localities up to 80 percent of the adult population showing immunologic evidence of such infection, and that many of these infected but asymptomatic individuals also had atrophic chorioretinal scars indicative of healed granulomatous lesions. However, since the *Histoplasma capsulatum* had never been found on the routine examination of granulomatous lesions in eyes enucleated for uveitis or other causes, there was no actual proof of the relationship between this fungus and any ocular disease. Nevertheless, the suspicion of such an etiologic relationship remained alive because it was known that both in the systemic lesions of the benign clinical disease, and also in experimentally produced ocular lesions, the fungus disappeared early from the lesions and after a few months could not be demonstrated in sections.

Beginning around 1950, when histoplasmin became available for diagnostic purposes, more detailed studies for benign histoplasmosis were added to the routine diagnostic study made on uveitis patients in the Wilmer Institute. Up to 1959, approximately 400 patients with granulomatous uveitis had been so studied and 187 of these had shown positive histoplasmin tests. This material was then assembled and analyzed. It was found that 19 of these 187 histoplasmin reactors had an almost identical ocular picture—small, yellowish, scantily pigmented, focal lesions in the peripheral fundus, with the later development of a central cystic lesion in the foveal or perifoveal region. In about one half of these cases, the central lesion was later complicated by a collarette of hemorrhage.

All of these 19 patients had the accepted picture of benign, systemic histoplasmosis—hypersensitivity to histoplasmin, spotty pulmonary calcification, and usually anergy to tuberculin. In nine of them, an exhaustive diagnostic survey had failed to reveal evidence of any other granulomatous disease to which the uveal lesions could be attributed. One of these patients showed a focal reaction around the ocular lesions after a diagnostic injection of histoplasmin. The remaining 10 patients with this ocular picture had immunologic evidence of other granulomatous infections. However, the ocular lesions in these 10 patients were totally dissimilar to those seen in toxoplasmosis, tuberculosis, or syphilis, and it was believed that the immunologic evidence of these other infections was unrelated to their granulomatous uveitis.

From these observations it was concluded that benign, asymptomatic histoplasmosis was an almost certain cause of a specific type of chorioretinopathy, and that in 10 percent of these 187 patients with positive histoplasmin reactions, or in four percent of the total number of patients with granulomatous uveitis, benign histoplasmosis was the actual etiologic cause of the ocular inflammation. The hypothesis was advanced that the peripheral

focal lesions were the result of small granulomatous lesions which had developed in the early stages of the infection when the parasitemia is known to be widespread, that as a result of this a sensitization of the ocular tissues had occurred, and the later central cystic lesions were probably manifestations of an allergic inflammatory reaction. More recent observations in other clinics, and especially the favorable results which have followed desensitization with histoplasmin in these cases, have supported these conclusions.

HOOKWORM LARVAE INFESTATION

Since 1932 it had been known that the *Onchocerca volvulus* was a frequent intra-ocular invader, and that in addition to the conjunctival and corneal lesions it might cause a peculiar form of chorioretinitis. It was also recognized that certain nematode larvae, notably those of *T. solium* and *T. echinococcus* occasionally invaded the eye. However, in the United States, and probably in other temperate zones, these nematode infestations were rare and unimportant causes of uveitis.

The discovery by Wilder (1952) of hookworm larvae in 22 of 44 eyes enucleated from children on a mistaken diagnosis of retinal blastoma or Coats' disease, sharply focused attention on the possibility that infection with such larvae might be an important cause of granulomatous inflammation in the eyes of children. Wilder was able to trace the migration tract of these parasites from the choroid where they caused a granulomatous inflammation, through to their final resting place in the vitreous, where in the course of their disintegration, they produced the histologic picture of an eosinophilic abscess surrounded by a granulomatous reaction.

Later investigations by Nichols and others have established that these larvae are usually those of *T. canium*. While this species of hookworm is nonpathogenic for man as an intestinal parasite, it is an extremely frequent one in domestic animals, dogs, cats, and

TABLE 1
PERCENTAGE INCIDENCE OF ADULT GRANULOMATOUS UVEITIS ASCRIBED TO
DIFFERENT ETIOLOGIES FROM 1941 TO 1960

Etiologic Factor	Series I	Series II	Series III	Series IV	Series V
	Guyton and Woods, 1941* 348 Cases	Woods and Guyton, 1944 157 Cases	Woods, et al., 1954 191 Cases	Jacobs, et al., 1956 107 Cases	Woods, 1960 134 Cases
	%	%	%	%	%
Tuberculosis	80	52	23	22	20
Syphilis	17	17	7	4	2
Sarcoidosis	1	10	6	5	3
Brucellosis	0.7	10	7	3	2
Toxoplasmosis	0	0	25	35	36
Histoplasmosis	0	0	0	0	13
Miscellaneous	1.3	5	13	4	2
Undetermined	0*	6	19	27	22†

* Tentative or presumptive diagnoses were assigned to all cases in Series I.

† Includes 29 cases in which differential diagnosis lay between tuberculosis and toxoplasmosis.

so forth. The larvae are abundant in the feces of these animals. Human infestation with these larvae may be acquired either by oral ingestion of contaminated food, or by the parasite entering through cuts or abrasions on the feet, especially in bare-footed children. The larvae do not develop in the gastrointestinal tract, but are carried by the circulation to the somatic tissues where they die and disintegrate.

Wilder's demonstration that they may also frequently be deposited in the eye added another agent to the possible causes of endogenous ocular disease. While infestation with hookworm larvae is probably a rare cause of adult granulomatous uveitis, it must be considered as a possible factor in the granulomatous uveitis of children, especially when there are any associated symptoms suggestive of either retinal blastoma or Coats' disease.

In addition to the increase in our knowledge of the pathogenic agents which may cause a granulomatous uveitis, the use of newer diagnostic procedures—the therapeutic trial test for tuberculosis, specific antibody tests for syphilis, the fluorescent antibody test, the realization of the significance of plasma cells, and so forth—have contributed to our knowledge of the etiology and pathogenesis of granulomatous uveitis, and

have radically altered our earlier concepts of the relative importance of the various etiologic agents. How great this change has been is well illustrated by the five successive studies on the etiology of uveitis from the Wilmer Institute.

In the 1941 report, already alluded to, tuberculosis was considered the etiologic factor in 80 percent of the cases of granulomatous uveitis, syphilis in 17 percent and other causes in only three percent. In the 1944 report, when consideration was given to sarcoidosis and brucellosis, the figure ascribed to tuberculosis fell to 52 percent, and in the last three reports, which comprise 432 cases seen from approximately 1950 to 1960 and in which all the now recognized etiologic factors were considered, the figures were still further radically altered. A summary of these five reports is shown in Table 1.

In Table 2 are shown the number of cases and the percentage incidence ascribed to various etiologies in 432 cases of adult granulomatous uveitis seen from approximately 1950 to 1960. These are the cases in the last three studies in Table 1 and are the only cases in which acquired toxoplasmosis and benign histoplasmosis were considered.

In this summary (table 2) tuberculosis has yielded first place to toxoplasmosis, and

these two etiologies are responsible for over 50 percent of the cases. If the 29 cases in which the differential diagnosis lay between tuberculosis and toxoplasmosis are considered here, then the percentage incidence of granulomatous uveitis due to these two causes rises to approximately 60 percent.

The fall in the percentage incidence of cases ascribed to syphilis from 17 percent in the 1941 and 1944 reports, to the low figure of 4.6 percent in the cases seen from 1950 to 1960, is an accurate reflection of the control of syphilis by penicillin in the last decade. The over-all percentage incidences of sarcoidosis, brucellosis, and histoplasmosis as etiologic factors are reasonably consistent throughout in these 432 cases, and for the present may be regarded as close to correct. There are insufficient cases in the miscellaneous group to permit any conclusions. It is interesting that with the most complete surveys practical, there is still a 15.5 percent incidence of cases in which no etiologic diagnosis is possible. If even stricter diagnostic criteria are demanded, this figure will be proportionally higher.

NONGRANULOMATOUS UVEITIS

The original concept that nongranulomatous uveitis is a hypersensitivity reaction is based solely on the clinical picture, on the

TABLE 2

NUMBER OF CASES AND PERCENTAGE INCIDENCE OF CASES ASCRIBED TO VARIOUS ETIOLOGIC FACTORS IN 432 CASES OF GRANULOMATOUS UVEITIS STUDIED FROM 1950-60

Ascribed Etiology	No. of Cases	Percentage Incidence
Acquired toxoplasmosis	133	30.9
Tuberculosis	94	27.0
Toxoplasmosis or tuberculosis (differential diagnosis)	29	6.7
Syphilis	20	4.6
Sarcoidosis	19	4.4
Brucellosis	21	4.9
Histoplasmosis	17	3.9
Miscellaneous (S.O., viruses, etc.)	32	7.4
Undetermined	67	15.5
	432	100%

apparent sterility of the aqueous and uveal tissue, and on experimental analogy. No specific hypersensitivity had been demonstrated in patients with this form of uveitis and the nature of the possible allergens was unknown. The occasional apparent relationship of the uveal inflammation to some systemic or focal infectious process suggested it might at times be due to a bacterial type of sensitivity. The significance of the mobilization of plasma cells and their relation to antibody formation was then unknown, and consequently, there was no recognized histologic evidence of hypersensitivity. However, within the last two decades, extensive investigations have produced considerable evidence which supports the original hypothesis. This supporting evidence may be listed as follows:

1. Evidence of an undue hypersensitivity to protein and bacterial antigens in patients with nongranulomatous uveitis.
2. The results of specific bacterial desensitization in patients with nongranulomatous uveitis.
3. Evidence of a prior streptococcal infection in patients with nongranulomatous uveitis.
4. Immunologic evidence of a local antibody concentration in the eyes of experimental animals and patients with nongranulomatous uveitis.
5. Histologic evidence of local antibody formation in the sensitized eyes of experimental animals.

1. HYPERSENSITIVITY IN PATIENTS WITH NONGRANULOMATOUS UVEITIS

A. Air-borne allergens—foods. There are a few scattered reports of nongranulomatous uveitis associated with hypersensitivity to pollens, animal dander, and so forth, and to various foods. Isolation of the patients from the incriminated allergen and occasionally desensitization resulted in a clinical improvement in these patients. The etiologic diagnosis in these cases was based solely on clinical observation and the demonstration of a cutaneous hypersensitivity and was not sup-

ported by the exclusion of other possible etiologic factors, immunologic studies, or animal experimentation. However, a few of these reported cases are so dramatic that they are almost convincing. Hypersensitivity to this group of allergens may well be an occasional cause of nongranulomatous uveitis.

B. *Drugs—proteins.* Nongranulomatous uveitis due to a hypersensitivity to various drugs has been reported. It has been known for years that alkaloids, and even inert metals, may combine with the host's native protein and form foreign antigens. The great majority of ocular reactions to such antigens result from the direct instillation of the drug into the conjunctival sac, and the concomitant contact dermatitis and conjunctivitis leave no doubt as to the etiologic diagnosis. Others, attributed to the oral ingestion of drugs such as sulfonamides, and so forth, are not so convincing.

A quiet, mild, nongranulomatous uveitis is frequently seen in patients with serum sickness, and in these cases the occurrence of the ocular reaction with concomitant systemic symptoms leaves little doubt that the eye has participated in a generalized hypersensitivity reaction to the foreign serum protein.

C. *Bacterial antigens.* While it is probably true that rare cases of nongranulomatous uveitis may be dependent upon a hypersensitivity to air-borne allergens or to foods, and it is certainly true that occasional cases are reactions due to a drug or to some protein hypersensitivity, the weight of evidence clearly indicates that hypersensitivity to bacterial antigens, and possibly to some viral antigens, is by far the most important factor in the etiology of nongranulomatous uveitis.

Contact of the tissues with any pathogenic bacteria, or indeed theoretically with non-pathogens, may result in sensitization to the specific bacterial protein. The immensity of the problem of detecting a responsible bacterial hypersensitivity in any case of nongranulomatous uveitis is therefore apparent. While other organisms, notably the coliform and pleuropneumonia groups, have been sug-

gested as being responsible for the basic hypersensitivity, thus far the streptococci have been the only group extensively investigated. These organisms have been especially investigated for the reasons that (a) nongranulomatous uveitis is frequently associated with certain forms of rheumatic diseases which are believed by many to be in some way related to a previous streptococcal infection, and (b) barring the staphylococci which are usually secondary invaders, the streptococci are the organisms most frequently found in foci of infection.

1. *The question of streptococcal hypersensitivity* has been investigated in a large group of patients with nongranulomatous uveitis, using as controls a group of adult cataract patients with no history of streptococcal infection and a second group of patients with granulomatous uveitis in whom no undue bacterial hypersensitivity would be suspected. These various groups of patients were tested against a battery of some 60-odd strains of antigenically distinct streptococci and occasionally to autogenous organisms (see later). As far as possible all reasonable precautions were taken to avoid false-positive reactions. It was found that in the control group of cataract patients the incidence of positive reactions to one or more of the stock streptococcal antigens was 22 percent, in patients with granulomatous uveitis it was 27 percent, while in patients with nongranulomatous uveitis it was 80 percent. These results are shown in Table 3.

The 22 to 27 percent incidence of positive reactions in the control groups appears to represent the error inherent in this procedure—the incidence of such a bacterial hypersensitivity in the normal population. This same error is reflected in the percentage failure rate (22 percent) in patients with nongranulomatous uveitis who were proven hypersensitive to streptococcal antigens, were given desensitization therapy, but in whom such treatment was a complete failure. In these patients the demonstrated hypersensitivity was obviously unrelated to the uveitis, and

TABLE 3

INCIDENCE OF UNDUE STREPTOCOCCAL SENSITIVITY IN CONTROL GROUPS AND IN PATIENTS WITH NONGRANULOMATOUS UVEITIS

Type of Group	No. of Patients	Number and Percentage of Positive Reactions to Streptococci	Percentage of Negative Reactions
Controls (cataract patients)	100	22 or 22%	78
Controls (granulomatous uveitis)	297*	79 or 27%	73
Nongranulomatous uveitis	291†	231 or 80%	20

* 185 reported up to 1956; 112 studied 1956-60.

† 198 reported up to 1956; 93 studied 1956-60.

the responsible hypersensitivity—be it to some bacteria not included in the diagnostic kit, or to some nonbacterial antigen—was undetected.

Hypersensitivity to organisms cultured from the patients own foci of infection is of especial interest. Of the 291 patients with nongranulomatous uveitis tested for bacterial hypersensitivity with the stock battery of vaccines, 68 were also tested with vaccines prepared from organisms isolated from their own foci of infection. In the early stages of this study, all autogenous organisms so cultured were isolated in pure culture and individual test vaccines prepared from each. Failing to find significant reactions except those to streptococci or *Ps. aeruginosa*, after 1953 autogenous vaccines were prepared only from these two organisms. There were 40 positive reactions to these vaccines—31 to

alpha, three to beta, three to gamma streptococci, and three to vaccines from *Pseudomonas* organisms. It is especially noteworthy that 15 of these 40 positive reactors gave negative intracutaneous tests to all the streptococcal strains in the stock diagnostic kit, while they gave two plus (++) or stronger reactions to the autogenous streptococci recovered from their own foci of infection. Ten of these patients were treated and did exceptionally well on desensitization with vaccines consisting of their own autogenous organisms. Had the bacterial flora of the discovered foci of infection not been cultured, and these 10 patients not tested against their own organisms, the therapeutic possibility of such specific desensitization would have been missed. The results of these sensitivity tests are given in Table 4.

2. The effect of specific desensitization.

TABLE 4

RESULTS OF INTRACUTANEOUS TEST WITH ORGANISMS CULTURED FROM FOCI OF INFECTION IN PATIENTS WITH NONGRANULOMATOUS UVEITIS

Series and No. of Patients	No. of Patients Tested	Results		Positive to Stock & Autogenous	Positive to Autogenous Only	Type of Organism Streptococci			Ps. Aeruginosa
		Positive	Negative			Alpha	Beta	Gamma	
I. Prior to 1953 101 patients	30	17	13	9	8	10	2	3	2
II. 1953-56 97 patients	17	12	5	8	4	11	0	0	1
III. 1956-60 93 patients	21	11	10	8	3	10	1	0	0
TOTALS 291 patients	68	40	28	25	15	31	3	3	3

TABLE 5
EFFECT OF SPECIFIC BACTERIAL DESENSITIZATION IN SEVERE, RECURRENT
NONGRANULOMATOUS UVEITIS

No.	Cases Treated	Posttreatment Period of Observation	Successes	Improved	Failures
1st Series	36	3-12 yr.	27*	3	6
2nd Series	50	6 mo.- 3 yr.	27	10	13
TOTALS	86	6 mo.-12 yr.	54 (63%)	13 (15%)	19 (22%)†

* In 10 cases late recurrences of uveitis after cessation of treatment synchronous with a return of the bacterial hypersensitivity.

† Includes three patients who abandoned treatment on account of focal ocular reactions.

If nongranulomatous uveitis is in truth a hypersensitive reaction dependent upon an underlying hypersensitivity to some allergen, the removal of the basic sensitivity should be accompanied by a cessation of the recurrent attacks as long as the desensitized status is maintained. There is no way to desensitize the uveal tissue other than as part of a general systemic desensitization. With a few scattered exceptions, specific systemic desensitization in nongranulomatous uveitis has been attempted only in patients with a proven bacterial hypersensitivity to streptococcal antigens, or to organisms isolated from their own foci of infection.

Up to 1956, desensitization with such specific bacterial vaccines had been employed as a therapeutic procedure in 86 patients with a severe, recurrent, nongranulomatous uveitis which had previously been resistant to the usual conventional therapy. In 54 of these patients desensitization, carried to the point where the patient no longer reacted to the test vaccines, was accompanied by a complete remission of the attacks as long as the desensitized status was maintained. In 13 patients, who were only partially desensitized, the attacks were of diminished severity and the intervals between attacks of longer duration. In the remaining 19 patients, 16 of whom appeared to be completely desensitized and three of whom abandoned treatment before desensitization could be accomplished, this therapeutic procedure was a failure. In

these 16 desensitized patients the demonstrated bacterial hypersensitivity was certainly unrelated to the uveitis. These results are shown in Table 5.

It should be noted that there is no control series in this study, and it is possible, although unlikely, that the favorable therapeutic result observed may have been due to some nonspecific action of the vaccines, or to some other unrecognized factor.

3. *Evidence of prior streptococcal infection.* The streptococci are complex antigens composed of various polysaccharides and endoprotein fractions. In addition, they secrete certain enzymatic substances, among the most important of which are a hyaluronidase and a lysin. After a streptococcal infection, inhibitory substances to these antigens appear in the blood stream and persist there for months or years after the patient has recovered from the original infection. The presence of these antibodies in the blood stream in any significant amount is regarded as an indication that at one time the patient has had a systemic streptococcal infection. These antibodies do not indicate and are not concerned with an active infection.

In the effort to demonstrate a prior streptococcal infection in patients with nongranulomatous uveitis, or acute iridocyclitis, a number of investigators have determined the antistreptolysin-O, and occasionally the anti-streptohyaluronidase, titers in such patients, and have compared these with similar titers

in supposedly normal individuals and in patients who have recovered from known streptococcal infections. The reported results have varied considerably, influenced possibly by the techniques employed, by the type of uveitis studied, and by the time which may have elapsed between a prior streptococcal infection and the uveitis. The antistreptolysin-O titer has been the one usually studied.

Some investigators have reported that patients with acute anterior iridocyclitis as a group show significantly higher titers than do normal individuals, but somewhat lower titers than patients who have recovered from acute rheumatic fever, and so forth. Others have reported either insignificant differences, or no difference at all between the titers of uveitis patients and normal controls. Those who have reported higher titers in uveitis patients as a group and who believe this finding may be suggestive of a streptogenic etiology for the uveitis, admit there is so much variation that the test is of little or no value in the particular patient.

It appears that the determination of the streptolysin-O titer in the blood plasma is at best a poor test either for the demonstration of a streptogenic etiology for the uveitis, or for a prior streptococcal infection in uveitis patients. It is quite possible, however, that the antistreptohyaluronidase titer may be more rewarding.

4. *Evidence of antibody concentration in the eye.* It has long been known that when an experimental animal, sensitized by intraocular injection of an antigen, is challenged by the parenteral injection of the same antigen, the eye will react with a violent inflammation while the animal shows little or no evidence of any systemic reaction. Similarly, patients with a presumed allergic iridocyclitis rarely show evidence of any systemic allergic disturbance. What is the reason for the increased vulnerability of the eye to antigenic challenge?

Various explanations have been offered: (a) that the anatomic structure of the eye, with its abundant smooth muscle and exten-

sive capillary bed, make it an admirable shock organ for the expression of allergic reactions; (b) that an increased vascularity resulting from the sensitizing injection or infection make it especially vulnerable to allergic shock; (c) that some preceding trauma has facilitated the passage of antibodies from the blood plasma to the ocular fluids; (d) that the reaction resulting from the original contact of the ocular tissues with the sensitizing antigen results in a local concentration of antibodies in the eye as compared to the systemic tissues.

Suffice to say that recent investigations have discounted, if not completely disproven, the first two hypotheses. There is, however, ample evidence that both preceding trauma and the inflammatory reaction resulting from contact of the uveal tissues with an antigen, result in an increased antibody content in the aqueous.

Early investigations (1908-1916) showed that in systemically immunized or sensitized animals, the antibody content of the primary aqueous is below that of the blood plasma but that, after paracentesis and drainage of the aqueous, the antibody content of the aqueous is greatly increased.

It has also been shown (MacLean, 1936) that when one eye of a systemically sensitized animal is subjected to a paracentesis, the traumatized eye will react with an iridocyclitis to a systemic injection of the challenging antigen, while the second, untraumatized eye will remain clear. The obvious explanation for this is that the iridocyclitis in the traumatized eye is due to an increased antibody content which resulted from the paracentesis.

This hypothesis was directly proven by Taylor and his associates. These investigators traumatized one eye of systemically sensitized rabbits by a standard, nonperforating procedure. They then demonstrated an increased antibody content in the aqueous of such eyes. When these animals were then challenged by a parenteral injection of the antigen, the eyes with the elevated antibody

content reacted with an acute iritis while the untraumatized eyes with the low antibody content remained quiet.

A local increase in antibodies was also demonstrated by Witmer (1955) in animals with a leptospiral uveitis induced by the direct injection of leptospira in the eye. Fourteen days after such inoculation a local accumulation of leptospiral agglutinins was observed in the aqueous and thereafter the aqueous titer exceeded that of the blood plasma by a 3:1 ratio. When a superimposed, sterile inflammation was produced in these eyes by the injection of an irritant, there was a still further increase in the aqueous anti-leptospiral agglutinins.

In 1958, Laffers and Bozsoky reported immunologic and chemical studies of the aqueous in patients with various forms of uveitis. In acute iridocyclitis they found both the antistreptolysin titer and the albumen content were significantly elevated. Since the titer in the second aqueous was essentially the same as in the first, they did not believe this increase in the antibody content was due to an increased capillary permeability at the blood-aqueous barrier. In their last communication they reported finding a sharply increased aqueous antistreptolysin titer in the aqueous of 14 out of a total of 21 patients with acute iridocyclitis, while the titer was normal in patients with other types of ocular disease and in their controls. They concluded that their observations indicated the probability of local antibody formation in the eye and that the finding of an increase in the antistreptolysin titer of the aqueous cemented the hypothesis of the streptogenic nature of the uveitis. On the other hand, Leopold and his coworkers found no significant elevation of the antistreptohyaluronidase titer in the aqueous of 25 patients with unspecified types of uveitis.

5. *Local antibody production in the eye.* It is now known that antibody is manufactured by the plasma cells and that a local concentration of plasma cells is indicative of antibody production. In Witmer's 1955 ex-

periments, he observed such a local accumulation of plasma cells in the eyes of animals with a leptospiral uveitis induced by the direct injection of leptospira in the eye. A further mobilization of these cells occurred when these eyes were later inflamed by the injection of a sterile irritant, and this in turn was accompanied by a further increase in the specific leptospiral antibodies. In later experiments Witmer demonstrated that the intraocular injection of purified egg albumen likewise led to a mobilization of plasma cells in the eye, and using the Coons' two-way fluorescent antibody technique, he was able to demonstrate actual specific antibody in the plasma cells infiltrating the uveal tract.

The recent experiments by Zimmerman and Silverstein, (1959) showed that the initial ocular response which followed the intravitreal injection of purified egg albumen was a mobilization of mononuclear cells—lymphocytes, plasmacytoid cells, and mononuclear phagocytes. Plasma cells appeared about the third day after the intravitreal injection and thereafter gradually supplanted the lymphocytes. Toward the end of the reaction the plasma cells were frequently the predominating cell. These plasma cells persisted in the eye through the full 64-day period of observation and were present when all antibody had disappeared from the blood stream. During this period the eye continued to react with renewed nongranulomatous inflammation to either the systemic or the intraocular injection of the antigen.

These are examples of the experiments which have demonstrated beyond reasonable question that a local production of antibody is stimulated within the eye by contact of the tissues with either an infectious antigen or by a sterile protein. Once such a local concentration of antibody has been effected, it persists for an indefinite period of time, exceeds the titer in the blood plasma, and thereafter renders the eye especially vulnerable to antigenic challenge. Thus the old term "elective sensitization of the eye" appears finally to have been vindicated.

On a critical review of this comparatively recent work, it is obvious that the material as a whole gives strong support to the original premise that nongranulomatous uveitis is a hypersensitive reaction, yet no individual piece of evidence is in itself conclusive. It is well known that various species of animals and man may react in quite different manners to infections and insults. Furthermore, it appears that there are only a limited number of ways in which the eye can react to insult. It is therefore dangerous to draw sweeping conclusions on the etiology of disease from animal experimentation. The clinical studies in patients are open to the criticism that there is an admitted large error of unrelated positive reactions in the sensitivity studies, and there is the possibility that the results observed in desensitization therapy may be due to some nonspecific action of the vaccine injections. Nevertheless, despite these criticisms, the sum-total of these observations is strong, indeed almost convincing, evidence of the validity of the original hypothesis.

MIXED UVEITIS

The mixed type of uveitis may arise under the following circumstances:

A. *A pathogen* which primarily excites a granulomatous inflammation, at the same time may sensitize the ocular tissues to its specific protein. Once such sensitization has occurred, a reaction between the sensitized tissues and any antigen in the eye will result in an acute allergic inflammation superimposed on a basic granulomatous uveitis. A clinical example of this would be the sudden exacerbation of anterior uveal inflammation or choroidal edema in an eye with a torpid tuberculous uveitis. This may result from a reaction of the sensitized tissues either with residual antigen in the eye, or with soluble antigen reaching the eye from a systemic focus, or from an exogenous source. An example of the latter would be the "focal reaction" induced in the tuberculous eye by the parenteral injection of an excessive dose of tuberculin.

B. *A prior unknown or unrecognized infection* may leave the ocular tissues sensitized to the specific protein of a pathogen causing granulomatous disease. A later reinfection of such a sensitized eye with this same pathogen would be heralded by an acute allergic inflammation. The actual basic granulomatous nature of the uveitis would only be recognized when the pathogen later seeds out and produces its characteristic lesions.

C. *Sterile, particulate matter which acts either as a foreign antigen or as a toxic substance*, that is, lens material or degenerating collagen, may excite a primary nongranulomatous inflammation. This same foreign or toxic material may also stimulate a mobilization of phagocytic cells for their routine duty of policing up the premises. Such responses would result in the clinical and histologic picture of a mixed uveitis.

D. *In rare instances a palisading epithelioid cell reaction* may occur in an eye which has been the site of a prolonged nongranulomatous inflammation. The reason for this late reaction is unknown.

In the first category, the clinical picture of a sudden, superimposed, acute inflammation in eyes with a granulomatous uveitis, and the focal reactions in a tuberculous eye induced by the parenteral injection of an excessive dose of tuberculin, are so well known they require no comment. Experimentally, such focal reactions can regularly be produced in immune-allergic rabbits with a healed or quiescent secondary ocular tuberculosis by the intraperitoneal injection of a proper dose of tuberculin.

The "pars planitis" or "peripheral anterior chorioretinitis," so well described by Schepens and his associates (1950-56-60) and by Welch (1960) may well be an example of this type of mixed uveitis. The fundus lesions of this pars planitis can be visualized only by using scleral depression and indirect binocular ophthalmoscopy. The basic lesion is a massive, often nodular, or at times a diffuse, exudate over the region of the ora serrata or pars plana. This lesion is classified by Schep-



Fig. 1 (Woods). Focal granulomatous lesion of the pars plana, with epithelioid and giant cells. (A.F.I.P. Accession No. 294577.)

ens clinically as a granulomatous one. It is often complicated by minor peripheral vascular changes, choroidal edema of the posterior pole, and sometimes by what appears to be clearly a nongranulomatous iridocyclitis. No specific etiology for this pars planitis has been established.

An eye in which this diagnosis has been made clinically has not as yet come to section, so there is no known material available for histologic study. However, ophthalmic pathologists, in the routine examination of autopsy eyes or in eyes enucleated for unrelated causes, have occasionally observed old, focal, granulomatous lesions in the region of the pars plana and evidences of an associated nongranulomatous iridocyclitis. An example of such an eye is A.F.I.P. Accession No. 294577. The clinical picture of this eye is largely unknown. In the pars plana there is an old, necrotic, focal granulomatous lesion with palisading epithelioid cells, giant cells, and necrosis of the pigment epithelium. Adjacent is an area of lymphocytic and plasma cell infiltration (figs. 1 and 2). Anteriorly, in both the homolateral and contralateral iris, there is an extensive round-cell infiltration with many plasma cells (fig. 3). Under high power, typical Russell bodies can be

identified (fig. 4). In short, the picture is that of a mixed uveitis, with a typical focal granulomatous lesion in the pars plana, and an equally typical, active, nongranulomatous iridocyclitis. No pathogens could be found in the granulomatous lesion. One might suspect that it was originally a histoplasma lesion, and that, as would be expected, the fungus has now disappeared. However, this is only a suspicion.

The obvious explanation for this histologic picture is that, whatever the original pathogen may have been, in addition to the basic granulomatous lesion of the pars plana, it had produced a sensitization of the anterior uvea and the nongranulomatous iridocyclitis represents an allergic reaction between the sensitized tissues and residual antigen. Thus this histologically diagnosed pars planitis would belong to the first category of mixed uveitis.

In the second category, a uveitis beginning as an acute, nongranulomatous iridocyclitis, and later developing into a typical generalized granulomatous uveitis, is probably a rare occurrence. However, a classical example of this picture was reported in 1956. An adult patient with a proven, apparently arrested, pulmonary tuberculosis, suddenly developed

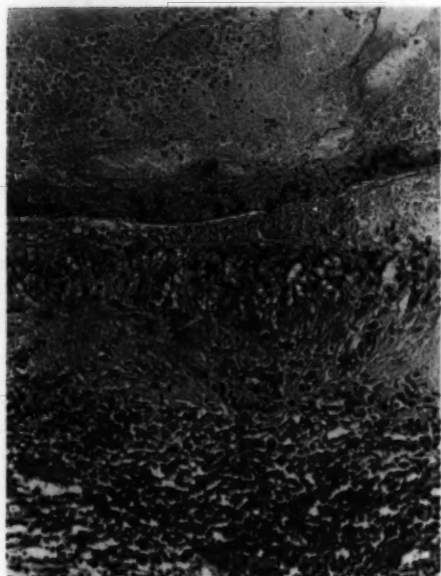


Fig. 2 (Woods). Another view of the section in Figure 1, showing palisading epithelioid cells and necrosis of pigment epithelium, and adjacent non-granulomatous reaction. (A.F.I.P. Accession No. 294577.)

an acute iridocyclitis. This was controlled with corticosteroids. Some two weeks later, the eye developed a typical generalized granu-

lomatous uveitis, with mutton-fat keratic deposits, Koeppe nodules, and miliary tubercles throughout the fundus.

Lens-induced uveitis, whether it be attributed to the supposed toxic action of degenerating hypermature lens material (phacotoxic uveitis) or to the organ-specific antigenic properties of lens protein (endophthalmitis phacoanaphylactica) is an example of a mixed uveitis caused by foreign particulate matter. Another example of mixed uveitis is when degenerating collagen tissues excite a focal surrounding epithelioid cell reaction.

The palisading epithelioid cell reaction in prolonged allergic inflammation was first described by Rich, et al., in an experimental systemic lesion. These authors thought perhaps it resulted from the persistence of circulating antigen after sensitization had been established. Similar pictures in a human eye with a prolonged nongranulomatous iridocyclitis, and in experimental eyes with a chronic allergic uveitis were reported in 1955 (Woods, Friedenwald, and Wood), but Rich's suggestion could not be validated, and no other cause could be found. In 1959, Zimmerman and Silverstein observed this reaction in the eye of one of their experimental animals but could offer no explanation for it.

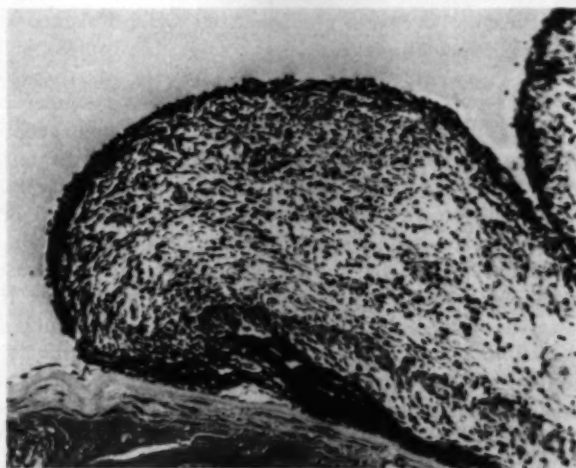


Fig. 3 (Woods). Nongranulomatous inflammation of homolateral iris, showing plasma cells, lymphocytes, and Russell body. (A.F.I.P. Accession No. 294577.)

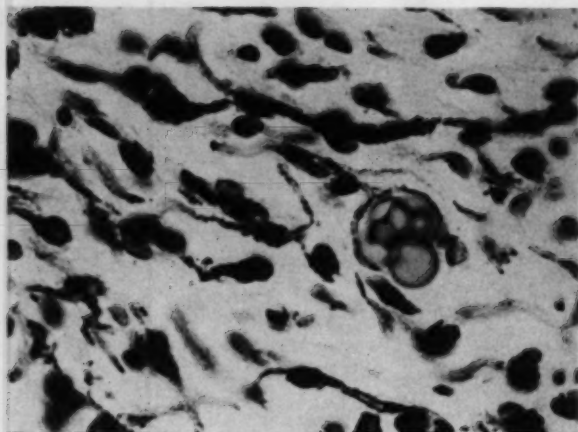


Fig. 4 (Woods). High-power view of Figure 3, showing morphology of cells and Russell body. (A.F.I.P. Accession No. 294577.)

All that can now be said is that it is a rare occurrence for which there is as yet no adequate explanation.

It is quite possible that in addition to these four pathogeneses, there may also be other causes for this mixed and confused type of uveitis. The four types of mixed uveitis here listed, however, can be identified clinically, and are established by histologic examination. Their recognition, and an understanding of the mechanism whereby they develop, will help clarify the confusion caused by a changing clinical picture and will aid in the differential diagnosis between granulomatous and nongranulomatous uveitis.

COMMENT

In this address little mention has been made of a possible viral etiology for either granulomatous or nongranulomatous uveitis. Extensive investigations have shown that some viruses can live and propagate in the eye and that a few of these may cause granulomatous inflammation. It is also known that nongranulomatous uveitis is frequently seen in association with a number of mild systemic viral infections. In these cases it has usually been impossible to isolate the living virus from the ocular tissues or fluids, and it is assumed that the nongranulomatous inflammation results

from the antigenic or toxic properties of the virus. But this is unproven and it is a fair statement that thus far the investigation of viral uveitis has presented an almost insoluble problem. This is one of the major unknowns in the etiology of uveitis.

There are still many other unknowns. There are undoubtedly still other undiscovered causes for granulomatous uveitis. Despite years of intensive investigation, the actual causes of sympathetic ophthalmia and sarcoidosis are as yet unknown. Even with the recognized causes, the differential diagnosis and identification of the exact etiology is often impossible. New weapons are needed in our diagnostic armamentarium.

Similar problems exist in nongranulomatous uveitis. The possibility that some cases may be caused by action of bacterial lipid and polysaccharide endotoxins is a completely unexplored field. There is the possibility that living, nonpathogenic agents, such as symbiotic viruses, may be the allergens responsible for the hypersensitive reaction. And when all is said and done, the final proof that nongranulomatous uveitis is a hypersensitivity inflammation will be the demonstration of the antigen-antibody union in the actively inflamed human eye.

These are all problems for the younger in-

vestigators of today and tomorrow. The start has already been made. As new approaches are developed and improved techniques are devised, it is a reasonable assumption that

these and similar problems will be solved and the etiology of uveitis will ultimately be completely clarified.

The Johns Hopkins Hospital (5).

A CASE OF MARFAN'S SYNDROME WITH BILATERAL GLAUCOMA*

WITH DESCRIPTION OF A NEW TYPE OF OPERATION FOR DEVELOPMENTAL GLAUCOMA
(TRABECULOTOMY AB EXTERNO)

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Glaucoma, though relatively infrequent, has been described among the many ocular manifestations in the Marfan syndrome.¹ In view of the structural abnormalities found regularly in the chamber angle, ciliary body and iris of these patients (Theobald,² Reeh and Lehman,³ deBuen and Velázquez,⁴ Burian and Allen,⁵ Burian,⁶ von Noorden and Schultz⁷) it is not surprising that in some of them there should be an increase in intraocular pressure.

I have had the opportunity to observe such a patient.[†] Her history, together with a description of a new type of operation devised for developmental glaucoma is being reported in this paper.

CASE REPORT

The patient, a 17-year-old white girl, was first seen on March 21, 1960. She had the typical habitus of a patient with Marfan's syndrome. She was five ft. 10 in. tall and weighed 148 lb. The referring doctor had cared for the eyes of the patient since 1951. At that time he found that she had subluxated lenses and had been using Pilocarpine drops (two percent) in each eye for some months, apparently in an attempt to avoid prolapse of the lenses into the anterior chamber. The vision was 6/60 in the right eye and 6/20 in the left, with -10D. sph., O.U. Pilocarpine was discontinued and the power of the lenses increased over the years. It was found later that the vision could be improved by correcting for the aphakic region of the pupil, with an eventual acuity of 6/9 in the right eye and 6/12 in the left.

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† The patient was kindly referred to me by Dr. Jack Dillahun, Albuquerque, New Mexico. I am under obligation to him for the excellent history and follow-up.

In June, 1959, the patient reported to the referring doctor with symptoms of acute glaucoma in both eyes which had occurred a few hours earlier and were subsiding at the time of the examination. The intraocular pressure was found to be 27 mm. Hg in the right eye and 37 mm. Hg in the left by Schiøtz tonometer and 21 mm. Hg in each eye by applanation tonometer. The attack of glaucoma appeared not to be lenticular in origin but, on gonioscopy, abnormal mesodermal tissue was seen to be covering the chamber angle.

At first 125 mg. of Diamox daily kept the intraocular pressure at normal levels, but the dosage of Diamox had to be increased until in January, 1960, 1,000 mg. daily were required to normalize the pressure which at that time tended to go as high as the lower 40's. Miotics could not be used, because of the drastic reduction in visual acuity which they caused by leaving the edge of the dislocated lens in the area of the miotic pupil.

It is of interest to note that the patient's mother was also afflicted with Marfan's syndrome. She was 45 years of age, and had had a cerebrovascular accident at the age of 40 years. She also had subluxated lenses. Her refractive correction and vision were O.D., -5.0D. sph. \ominus +2.0D. cyl. ax. 15° = 6/9 + 2; O.S., -3.0D. sph. = hand movements. The intraocular pressure was 20.6 mm. Hg in the right eye and 24.4 mm. Hg in the left. The chamber angles revealed changes which were quite similar to but less extensive than those of her daughter, which will be described. Although she had recovered to a considerable degree from her cerebrovascular accident, I refrained from a more detailed examination of her eyes because of her condition.

When I saw her daughter, her eyes were not irritated. The corneas, which had a horizontal diameter of 12 and 12.25 mm., respectively, and the limbus areas presented no abnormalities. The anterior chambers were rather deep, though irregular in depth. The color of the irises was yellowish-brown and the stromal layers were somewhat atrophic. The pupils were round, three to four mm. in size, and responded sluggishly to light and convergence. The lenses were dislocated templeward and downward and there was iridodonesis.

Gonioscopy showed that the angles were wide but irregular in width. But even where the dislocated lenses had caused a reduction in the width of the angles they were not really narrow. Nevertheless, though the chamber angles were wide, they were quite abnormal, as will be seen from their description.

Left eye, lower angle: the corneal wedge was of average shape. The anterior border of the trabecular zone was well defined by a fine dark gray line, made up in all probability of circular fibers but there was no prominence. Only the anterior one quarter of the trabecular area was exposed, the posterior three quarters were covered by a thin sheet of tissue representing a persistent adherence of the iris. This iris tissue appeared atrophic and showed areas of brown-black islands in which the pigment layer of the iris was seen through the extremely thin stroma. Three or four small vessels were seen in the thicker part of the stroma of this sheet. Posterior to this sheet, the iris became increasingly normal in appearance.

Left eye, upper angle: the corneal wedge was of average shape. The iris presented a persistent adherence as in the lower angle, but at the 12-o'clock position at least one half of the trabecular zone was exposed. Behind the thin sheet of iris tissue covering the angle, the iris came forward to an irregular border, taking in places the appearance of pectinate ligament structures. In other places the irregularities resembled iris processes and the iris tissues had somewhat of the frayed appearance seen in some cases of scoliosis.⁸ On the nasal side of the upper angle a vessel loop, probably part of the major circle, was exposed in the thin iris leaf covering the angle.

Left eye, nasal angle: appeared very much like the lower angle but three quarters of the trabecular area were hidden by the thin leaf of iris tissue.

Left eye, temporal angle: looked much like the lower and nasal angles, except that there were a number of irregularly directed vessels exposed in the thin iris tissue, having the appearance of pectinate ligament strands.

Right eye: all parts of the chamber angle had an appearance very similar to that in the left eye, except that an abnormally exposed circular vessel, probably part of the major circle, was seen in the upper and both lateral parts of the angle. The vessels were located near the edge of the persistent adherence of the iris, anteriorly to the region of Schlemm's canal of the trabecular band. The appearance of the nasal angle of the right eye is shown in Figure 1-A.

The fundi presented no particular abnormalities, there was no evidence of myopic or other degenerations. The discs showed physiologic cupping but were otherwise normal.

The visual acuity was: R.E., 6/9, L.E., 6/12, with the following correction: O.D., +6.25D. sph. \ominus +1.0D. cyl. ax. 113°; O.S., +5.75D. sph. \ominus +12.5D. cyl. ax. 40°. The patient wore an add of +5.0D. sph., O.U. Tangent screen visual fields presented a marked concentric restriction (five to 10

degrees for the 1/1,000 and 20 to 25 degrees for the 3/1,000 targets), but the blindspots were of normal size and shape.

The intraocular pressure was 14.6 mm. Hg in each eye when the patient was seen on March 21, 1960. Diamox was discontinued. On the following day the pressure readings were equal in each eye and measured 14.6 mm. Hg at 8:15 a.m., 34.4 mm. Hg at 2:15 p.m., and 31.8 mm. Hg at 4:00 p.m. Tonography, performed at 9:00 a.m. on March 23, 1960, gave C values of 0.06 for the right eye and 0.09 for the left with an initial P₀ of 22 and 21 mm. Hg, respectively. The patient was again placed on her regular Diamox routine.

COMMENT

It was clearly desirable to reduce the intraocular pressure surgically in this young girl. Miotics could not be used and the indefinite ingestion of the very high doses of Diamox did not seem advisable. In considering the type of operation to be performed, it appeared to me that it might be risky to do a goniotomy, because of the blood vessels seen gonioscopically in the thin tissue covering the angle and because of the likelihood that there were more extensive vessels hidden in this tissue. A cyclodialysis could have been attempted but it occurred to me that, in view of the dislocation of the lenses a trabeculodialysis, as suggested by Dellaporta,⁹ might be safer and more promising of success.

In discussing this matter with Mr. Lee Allen at some length, we decided that it might be advantageous to perform a trabeculotomy using the external approach. Mr. Allen accordingly prepared a special instrument for this purpose (fig. 2). This instrument consisted essentially of a narrow piece of stainless steel, bent so as to follow the curve of the limbus and provided with a blunt tip, and a handle appropriately angled with respect to the scyphelike curved part of the instrument. This part had no cutting edge. Two such instruments were available, one for right-handed, the other for left-handed use.

On March 25, 1960, a trabeculotomy ab externo was performed on the right eye. The operation will be briefly described here. The instrument itself as well as the technique of the operation have since been further de-

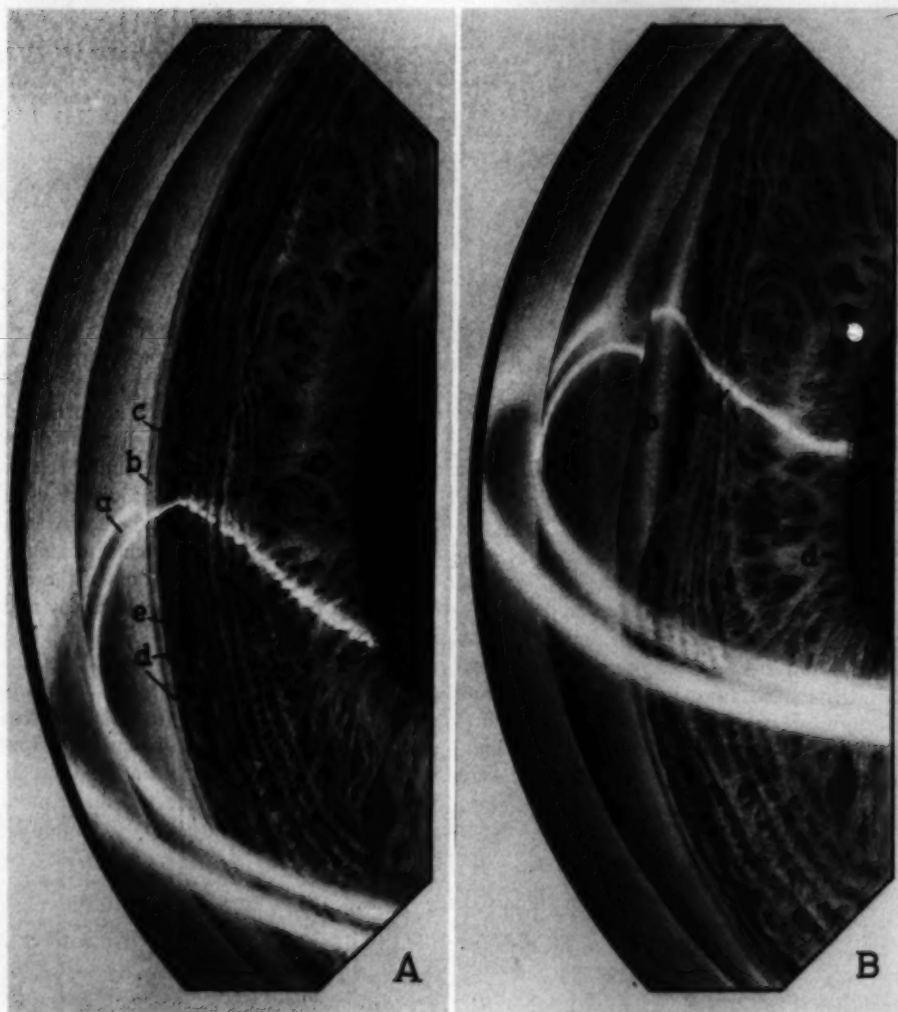


Fig. 1 (Burian). (A) Preoperative appearance of mirror view of nasal angle of the right eye. (a) Corneal wedge outlined by slitlamp beam. (b) Anterior one fourth of trabecular band. (c) Anterior edge of sheetlike persistence of iris. (d) Abnormally located and exposed circularly directed vessels. (e) Islands of blackish brown, indicating anteriorly positioned pigment layer of iris seen through extremely thin iris stroma. (f) Aphakic region of pupil.

(B) Appearance of mirror view of nasal angle of right eye on the 13th postoperative day. (a) Slit-lamp beam through area of trabeculotomy. (b) Area freed surgically of iris adherence and possibly of some layers of trabecular tissue. (c) Limited detachment of edge of Descemet's membrane. (d) Aphakic region of pupil.

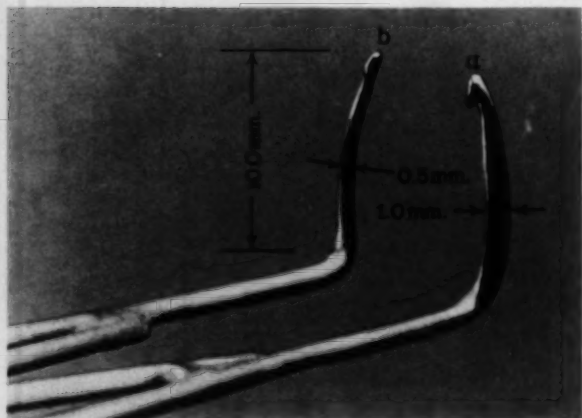


Fig. 2 (Burian). Trabeculotome used in the operations. (a) For thrust to the right. (b) For thrust to the left. Note especially the curve on the blade and its cross section flattened in such a way as to fit the plane of the scleral groove.

veloped and a more detailed description of the instruments and of experimental operations on eye-bank eyes and on eyes to be enucleated will be given in other publications.^{10, 11}

TECHNIQUE OF OPERATION

A limbus-based conjunctival flap approximately 10 mm. in width was turned down between the 3- and 2-o'clock positions. A black 4-0 silk suture was then placed superficially through the sclera about four mm. behind the limbus at the 3-o'clock position to simplify a radial incision through the sclera and to help spread the wound. The sclera was incised with a scleratome, starting in the gray band of tissue at the external limbus. The incision was carried back and carefully continued through the scleral tissue, until dark tissue of the uvea could be observed in the depth of the incision. At the limbal end the incision was continued in depth until it was felt that the trabeculotome could be introduced into trabecular tissue near the external wall of the scleral groove. The trabeculotome was then slowly advanced with rocking motions until all of the blade had been introduced. A check with a gonioscope showed slight pressure of the trabeculotome inward produced a bulge in the trabecular area. The pressure was then increased and the trabeculotome withdrawn from the wound with a sweeping motion. No aqueous was lost in

the procedure, nor was there any hemorrhage. The conjunctiva was closed with interrupted 6-0 catgut sutures over the unsutured sclera. The eye seemed to stand the procedure well. No mydriatics were given and the eye was covered with a simple eyepatch and shield.

There was no undue irritation of the eye on the first or second postoperative day and the patient was comfortable. On the third postoperative day (March 28, 1960) the right eye appeared quite clear and the patient was perfectly comfortable. The conjunctival flap was slightly soggy but there was no bleb formation. Gonioscopy was done and a layer of blood was seen in the upper and lower nasal angles but no real area of incision could be discerned at that time. The eye was mushy soft. However, since the Diamox medication had been stopped, the intraocular pressure of the left eye was around 35 mm. Hg. A trabeculotomy ab externo was, therefore, performed on March 29, 1960, on the left eye in the upper temporal quadrant. The surgical procedure was similar to the one in the right eye, except that the scleral incision was made at the 12-o'clock position and that the sclera was sutured, in addition to the conjunctiva. On that day a small hyphema was noted in the right eye but the patient was comfortable. Most likely, the gonioscopy on the preceding day had been premature.

The postoperative course in the left eye

was uneventful and remained so until discharge. It was rather stormy in the right. The anterior chamber showed diffuse cloudiness from a slight hyphema but it cleared considerably, day by day, and the eye was never uncomfortable. On April 7, 1960, the intraocular pressure at 3:00 p.m. was 8.5 mm. Hg in the right eye and 10.2 mm. Hg in the left. Both eyes showed only minimal irritation. There was no discomfort. Gonioscopy was done and the angles could be clearly observed. The operative area in the right eye, seen in the nasal angle, showed that, in an area from about 12:30- to 3:30-o'clock positions, the abnormal iris tissue covering the trabecular zone had been stripped down, but there was also some curling up of Descemet's membrane in this area (fig. 1-B). In the upper angle of the left eye a similar stripping of the mesodermal tissue from the trabecular zone between the 11- and 1-o'clock positions had been achieved but there was, in addition, what appeared to be a round opening in the remaining trabecular tissue at the 12-o'clock position. This hole was as interpreted as representing an opening into Schlemm's canal (fig. 3).

In the evening of that day (April 7, 1960) the patient developed severe pain in the right eye, with pain in back of her head and vom-

iting. The eyeball was not injected, the cornea was quite clear, and the anterior chamber showed only the very slight, diffuse haziness that was seen before. However, the intraocular pressure was in the neighborhood of 55 mm. Hg. Five hundred mg. of Diamox were immediately given intravenously, and 250 mg. every six hours by mouth. This resulted in relief of pain and a drop in intraocular pressure. However, on the morning of April 9, 1960, the lids of the right eye were swollen and there was a pronounced glassy edema of the conjunctiva. In spite of this the patient was perfectly comfortable and had passed a restful night. Cornea and anterior chamber of the right eye were clear. Local hydrocortisone drops (2.5 percent) were applied throughout the day and on the morning of April 10, 1960, there was no sign of edema either of the lids or of the conjunctiva of the right eye. Both eyes were slightly injected in the operative area but otherwise quiescent, the corneas and anterior chambers were clear. There was no sign of external filtration. The intraocular pressure was 4.9 mm. Hg in the right eye and 12.2 mm. Hg in the left. Diamox was discontinued.

The eye stayed comfortable, and on April 13, 1960, the intraocular pressure was 13.4 and 15.9 mm. Hg in the right eye and 10.2

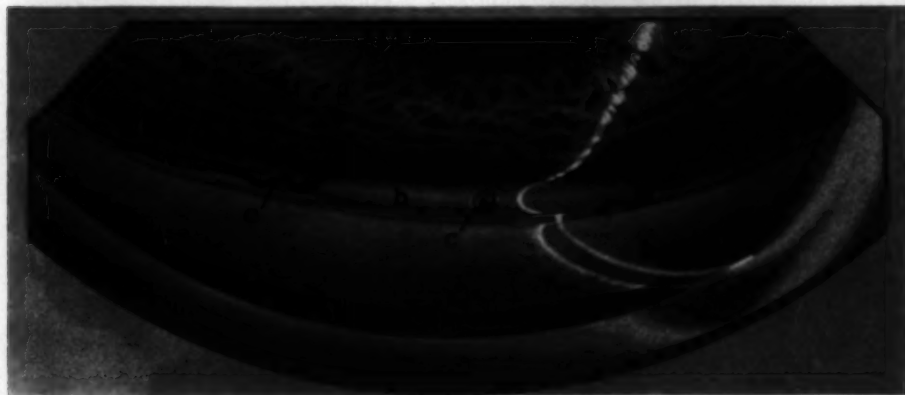


Fig. 3 (Burian). Appearance of mirror view of upper angle of left eye on the ninth postoperative day. (a) Sheetlike persistence of iris over posterior three fourths of trabecular band. (b) Area freed surgically of iris adherence. (c) Opening through trabecular tissue, probably into Schlemm's canal. (d) Aphakic region of pupil.

and 12.2 mm. Hg in the left, at 8:00 a.m. and 4:30 p.m., respectively, and the patient was discharged into the care of her physician on April 14, 1960. The visual acuity on that date was 6/12+2 in the right eye and 6/15+2 in the left with her own correction.

The referring doctor has informed me that, when the patient returned to him on April 18, 1960, the intraocular pressure was 32 mm. Hg in the right eye and 27 mm. Hg in the left (applanation tonometry). He prescribed Diamox (250 mg. twice daily). During the period of April 18, 1960, and June 28, 1960, the intraocular pressure varied between 11 and 15 mm. Hg in the right eye and 15 and 29 mm. Hg in the left. On August 1st the pressures were 10 and 9.0 mm. Hg, respectively. Diamox was discontinued. Thus far the intraocular pressure has remained within normal range without any medication. The vision, with a new correction of: O.D., +4.5D. sph. \ominus +1.0D. cyl. ax. 105° and O.S., +5.0D. sph. \ominus +1.25D. cyl. ax. 40° was 6/7.5 in the right eye and 6/12-2 in the left. The add was reduced to +3.0D. sph., O.U., and with it she obtained a reading acuity of Snellen 0.75 at 32 cm.

Up to the present the result obtained in this patient with the trabeculotomy ab externo has been very satisfactory. Should this result not prove to be permanent, I would not hesitate to repeat the operation in a different quadrant of the eye. However, I would restrain my curiosity and wait for at least two or three weeks before doing a postoperative gonioscopy.

SUMMARY

A case of a 17-year-old white girl with Marfan's syndrome and bilateral glaucoma is presented. The chamber angles showed a persistent adherence of the iris in the form of a thin sheet of tissue which left only the anterior one quarter of the trabecular area free.

This patient was treated by a new type of operation, designated as a trabeculotomy ab externo in which an appropriate instrument was introduced into the region of the canal of Schlemm and the trabecular area was incised.

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EXOPHTHALMOS-INHIBITING FACTOR IN NORMAL HUMAN SERUM*

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This study was undertaken in an attempt to uncover evidence of any factor in human serum which might help to explain the apparent contradictory aspects of thyroid ophthalmopathy. Foremost among these is the lack of correlation between the severity of the orbital process and the level of thyroid activity. Therefore, the suggestion that exophthalmos inhibition might be a characteristic of normal human serum seemed worthy of investigation.

METHOD

Specimens of *Fundulus heteroclitus* were obtained during the summer months of June, July, and August from the waters around New York City. They were kept in a plastic tank, which was subdivided into 12 compartments, each designed to hold one fish. The partitions between the compartments contained small holes, allowing free flow of the brackish water in which the fish were kept. Air was constantly bubbled through the water in each compartment, and the temperature was maintained between 19°C. and 22°C., by immersing the plastic tank in a larger glass aquarium through which tap water was continuously flowing. The fish were never kept more than five days.

The intercorneal distance was determined by a method previously described.¹ This consisted of placing the killifish underwater in a small laboratory fingerbowl, wedging wet pieces of gauze on each side, and then measuring the intercorneal distance monocularly with a loupe, by means of a Boley gauge (micrometer), held above the surface of the water. Readings were made to one tenth of a

mm. and the mean of seven readings was taken as the final measurement.

All injections were made intraperitoneally through the dorsal vent, employing a No. 27 gauge needle on a tuberculin syringe. Each injection was 0.25 cc. in volume, and each fish was injected once. Measurements were made at zero, two, four, and six hours.

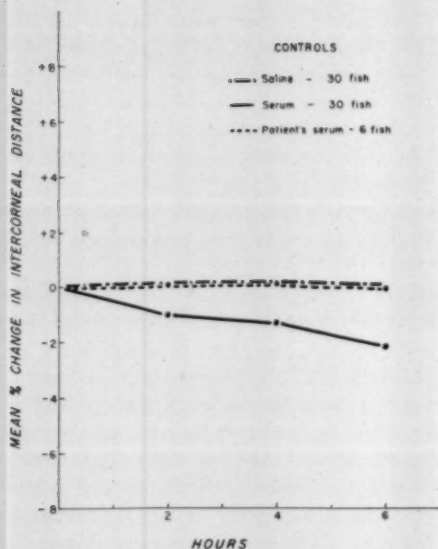
A total of 258 fish were employed. Some of the fish were injected with 0.85-percent saline solution, while others were injected with human serum obtained from normal individuals. In addition, sera from two patients with active, advancing thyroid ophthalmopathy were also employed. Various dosages of a beef anterior pituitary extract (Armour #317-51-R*), which was known to contain an active exophthalmos-producing substance for guinea pigs, were dissolved in these three media.

RESULTS

The results are summarized in Graphs 1 through 8. Graph 1 reveals that normal saline and the serum from one patient with advancing thyroid ophthalmopathy had no effect on the intercorneal distance, while the normal human serum had a definite enophthalmic effect. This presumably resulted from a non-specific toxic effect of the injection of a relatively large amount of foreign protein, which may be referred to as a "masking" effect. That it did not occur with the serum from the patient with active ophthalmopathy may or may not be significant. Serum from such patients has been said to produce exophthalmos in the *Fundulus*,² but repeated injections were employed and this finding has not been confirmed.³ It, therefore, seems unlikely that enough exophthalmos-producing substance

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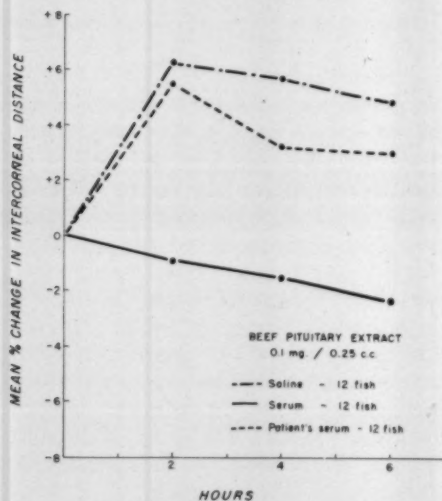
* Supplied through the courtesy of Dr. George Smelser.



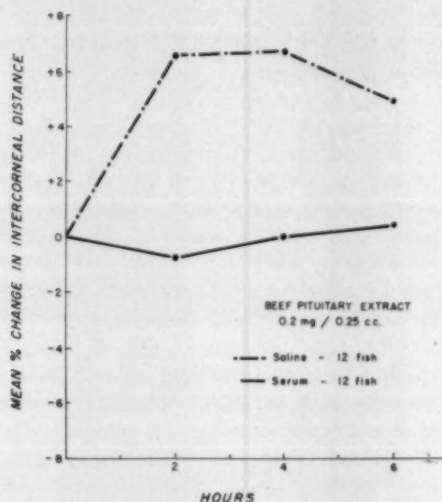
Graph 1 (Day and Nelson).

was present in 0.25 cc. of serum to offset the "masking" effect.

One-tenth mg. of the beef pituitary extract had a definite and pronounced exophthalmic effect when dissolved in saline or in serum

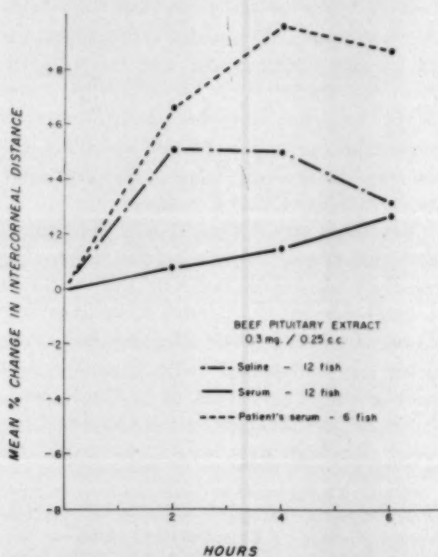


Graph 2 (Day and Nelson).

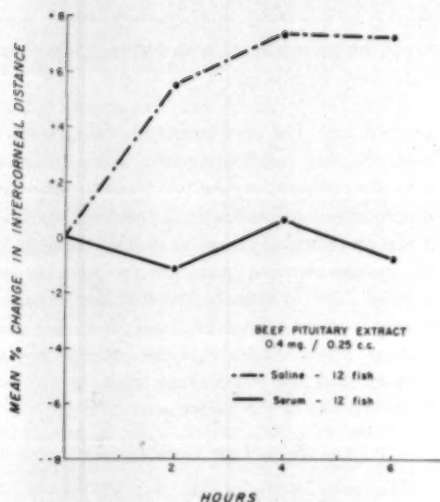


Graph 3 (Day and Nelson).

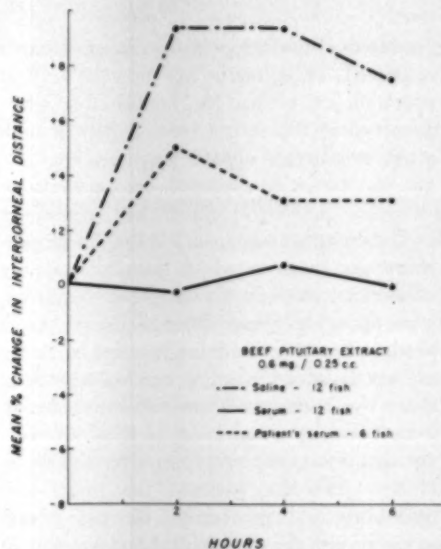
from a patient with active eye changes but it was without any effect when dissolved in normal human serum (graph 2). Two-tenths mg. was the level at which the exophthalmic substance in the beef pituitary neutralized the



Graph 4 (Day and Nelson).



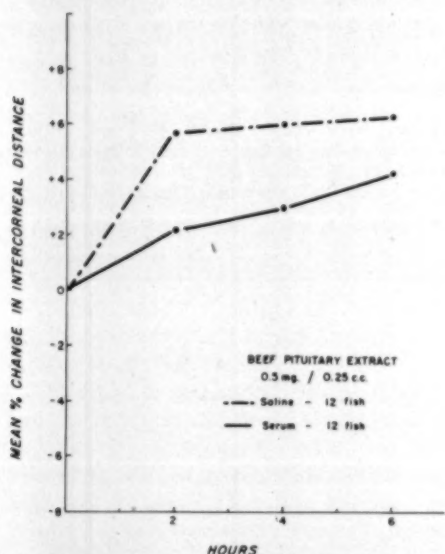
Graph 5 (Day and Nelson).



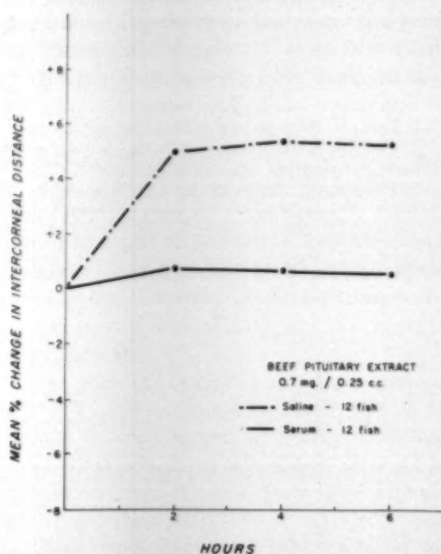
Graph 7 (Day and Nelson).

enophthalmic action of the normal serum (graph 3) and this exophthalmic effect increased to a dosage level of 0.6 mg. when the response was again neutralized (graphs 4

through 8). This latter may have resulted from the combined foreign-protein effect of the serum and the extract. When adminis-



Graph 6 (Day and Nelson).



Graph 8 (Day and Nelson).

tered in saline, however, the pituitary extract produced a marked proptosis in all dosages employed. Three-tenths mg. was the level at which the extract had its greatest effect when dissolved in the serum from a patient with active eye disease (graph 4).

DISCUSSION

The dosage levels from 0.2 to 0.5 mg. constitute the range in which the action of any unknown factors in human serum might become apparent. On an average, the proptosis produced in the Fundulus injected with the extract dissolved in saline reached a peak in about two hours, while the fish injected with extract in serum continued to show an average increase in the proptosis after that time. If the difference between the saline and serum injections represented the toxic effects of the serum, the intercorneal distance should not increase after the two-hour period. In the control studies with normal serum, the exophthalmic effect became continuously greater for six hours. Rather, this observation suggests that there may be some factor in normal human serum which "binds" the exophthalmos-producing substance and gradually releases it. No such binding action oc-

curred in the three instances where the sera from the two patients with active orbital disease were employed.

These observations must be considered as preliminary. The sera from only two patients with thyroid ophthalmopathy were utilized and the results of the study with normal serum are not conclusive. However, the implication that in thyroid eye disease there may be specific changes in the serum suggests an avenue for further investigation. Such changes would afford an explanation for the clinical observations that the orbital signs may precede, be concurrent with, or follow the treatment of the thyrotoxicosis.

SUMMARY AND CONCLUSIONS

The exophthalmic response in Fundulus heteroclitus of various dosage levels of beef anterior pituitary extract dissolved in saline, normal human serum, and in the sera of patients with active thyroid ophthalmopathy suggests that there may be some factor in normal human serum which "binds" exophthalmos-producing substance. This factor may be absent in the sera of patients with advancing ocular signs of thyroid dysfunction.
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OCULAR MANIFESTATIONS OF CHÉDIAK-HIGASHI SYNDROME*

REPORT OF A CASE WITH HISTOPATHOLOGIC EXAMINATION OF OCULAR TISSUES

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Chédiak¹ (Cuba, 1952) and Higashi² (Japan, 1954) first described the characteristic physical alterations which have come to be recognized as a familial syndrome. Cases have been reported by other authors^{3,4} between 1954 and the present.

Ocular abnormalities are almost always present. The eyes, however, never have been examined histologically. It is the purpose of this paper to report a typical case in which the clinical diagnosis was established and a careful examination of the eyes was accomplished. This is the first report of histopathologic examination of the eyes in this syndrome.

REVIEW OF LITERATURE

Chédiak and Higashi independently described families exhibiting anomalous granulations or inclusions in various types of leukocytes. A total of four children were involved in the family described by Chédiak, and all died before the age of seven years. The family described by Higashi was almost identical, with four affected children who died in childhood.

The parents were first cousins in the Cuban family, reported by Chédiak. They had 13 children, of whom two males and two females were affected.

In the Japanese family reported by Higashi, the parents were first cousins, once removed. Of the seven children in their family, two males and two females were affected.

The eight cases of Chédiak and Higashi had a fairer skin than their siblings and all had light or blond hair. Photophobia was present in all (suggesting that ocular albinism was present). One case described by Higashi showed pale fundi. Pigmentation of

the exposed areas of skin was observed, and in one case the diagnosis of xeroderma pigmentosum was made. Frequent infections were common in the eight cases and death usually followed an intercurrent infection. Generalized lymphadenopathy, abdominal distention and hepatosplenomegaly was a constant late finding. All cases had anemia, neutropenia and thrombopenia. Excessive sweating was noted in some cases.

Both Chédiak and Higashi described anomalous granulations in the polymorphonuclear leukocytes and lymphocytes in the peripheral blood, as well as abnormal "inclusionlike" bodies in the myeloid series in bone-marrow preparations.

Sato⁵ commented on the probable identity of the "new leukocytal anomaly" described by Chédiak, and the "congenital gigantism of peroxidase granules" reported by Higashi.

Post-mortem examination was not performed in any of the eight cases described by Chédiak and Higashi.

Autopsy reports have been made on two cases.^{3,4} Donohue and Bain³ described a case (a first-born child) which was of unusual interest in that the parents were unrelated. There was an absence of albinism; however, the child was photophobic and her hair was stated to be "fair," "very dry" and "sparse." Donohue and Bain³ cite personal communications from Söderhjelm, who observed a typical case in which the parents were unrelated.

The case of Donohue and Bain showed extensive infiltration of the brain and most organs by lymphocytes and some abnormal cells. These abnormal cells either were of the reticuloendothelial type or were large with almost "naked nuclei."

The case of Efrati and Jonas⁴ showed the clinical picture of leukemia, with immature and pathologic cells in the peripheral blood,

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anemia, thrombocytopenia, hepatosplenomegaly, and lymphadenopathy. This child was not an albino, and the parents were not related. One other child in this family was normal. Necropsy showed a malignant lymphoma with diffuse infiltration of all internal organs. The authors suggest that generalized changes in the reticulohistiocytic system are probably present in all cases.

The nature of the leukocytic inclusions is not known, and no other disease produces this change. Efrati and Jonas believe the inclusion bodies in the mononuclear cells to contain desoxyribose nucleic acid because of their chromatinlike purplish staining qualities.

CASE REPORT

N. W., a white male child, was born on November 26, 1954 (after a full-term, uneventful pregnancy). The birth weight was 7.0 lb. 1.0 oz. He was discharged from the hospital as a normal child.

Commencing at the age of one month, repeated bouts of respiratory infection occurred, for which tetracyclines and penicillin were administered. At two months of age, examination showed the spleen to be enlarged to three cm. below the costal margin.

In April 1955, at the age of five months, he was observed to have a right esotropia. Photophobia, an albinotic fundus reflex, and pale irises also were found.

At eight months of age (August 19, 1955) he was found to be well developed and in good health. The skin was normal; and his hair was of a light coarse "mouse" color. There was an alternating esotropia of 50 degree arc. The pupils showed an albinotic reflex, and the fundi were pale and poorly pigmented. A three-mm. recession of the medial rectus muscles was performed on July 10, 1956 (aged 20 months).

On April 1, 1957, refraction under general anesthesia showed: O.D., -6.5D. sph. \ominus +0.5D. cyl. ax. 90°; O.S., -6.0D. sph. \ominus +0.5D. cyl. ax. 90°. The fundi showed a marked lack of pigment. He had become quite photophobic by this time and the esotropia was still present.

At the age of 13 months, he was given antibiotic therapy for an otitis media and nasopharyngitis. The results were poor. A blood count was performed, and showed WBC 6800, 25-percent stab forms, three-percent polynuclear forms, and 91-percent lymphocytes. Inclusions were not described.

His condition improved, and he remained well except for minor infections until February, 1956, when he was first hospitalized for a severe respiratory infection. At this admission, the hemoglobin was 11.5 gm., WBC 11,000 with three-percent neutrophils, and 97-percent mononuclear cells. Platelets were adequate. Bone-marrow studies demonstrated

partial maturation arrest of the neutrophilic series. This picture was thought to be consistent with drug toxicity or poisoning. The following drugs had been administered: antihistamines, tetracyclines, erythromycin, penicillin, codeine, and bismuth.

Between March, 1956 and June, 1957, he was well. In June, 1957, physical examination revealed a well-nourished, healthy boy with a slightly pale skin. WBC were 8,250 with 14-percent neutrophils, platelets were 54,000. The ensuing months were characterized by tonsillitis, colds, ear infections, and persistent coryza. When examined in October, 1957, the spleen was five cm. below the costal margin.

In August, 1958 (aged three years, nine months), his right visual acuity was 20/70, and the left was 20/80. A bilateral resection of the external rectus muscle tendons was done on August 13, 1958. There was considerable postoperative reaction with excess granulation tissue at the surgical sites. Within a month this had cleared. Refraction subsequent to this showed only an increase in the astigmatic error in each eye to +2.25D. sph.

In February, 1959, he was hospitalized with severe tonsillitis. The liver and spleen were enlarged to two cm. below the costal margins. A one-cm. lymph node was found in the right axilla. Total WBC varied from 2,000 to 3,000 with two-percent to 15-percent polys. Lymphocytes averaged 80 percent. Many lymphocytes were atypical and exhibited magenta-colored cytoplasmic inclusions with the Wright stain, as did a few polymorphonuclear leukocytes. Bone survey was negative. Total protein was 6.3 gm. percent, albumin 2.3 gm. percent, and globulin 4.0 gm. percent. Cephalin flocculation was plus two. His condition gradually improved on antibiotic therapy.

When re-admitted in March, 1959, for a severe respiratory infection, he was wasted and pale. The abdomen was protuberant, due to enlargement of both the liver and spleen. Their lower borders extended to the umbilicus. The axillae contained small one-cm. lymph nodes. In spite of antibiotic therapy, the fever persisted. Blood cultures were negative. Dexamethasone (0.75 mg. q.i.d.) plus the usual antibiotics produced no appreciable change. He was discharged on June 6, 1959, still febrile.

While at home, the temperature rose repeatedly to 103°F., and the child had many aches and pains. On June 12, 1959, the dexamethasone was increased to 15.0 mg. q.i.d. Soon after this, the gums became swollen and hemorrhagic.

On June 27, 1959, he re-entered the hospital with an area of pneumonic infiltration in the right hilar area. The spleen extended into the left pelvis. Upon the suggestion of a hematologist, 300 cc. of the father's plasma was given intramuscularly in three daily injections in an attempt to produce antibodies specific to the patient's defect. Whole blood transfusions were also administered. WBC were 5,950 with eight-percent polys, and 92-percent mononuclear cells. There were three nucleated RBCs per 100 WBC. The lymphocytes still contained inclusion bodies. In order to alleviate the pressure symptoms, a splenectomy was performed on June 30, 1959. A

biopsy of the liver and removal of a node from a group of enlarged peri-aortic lymph nodes also was done. The child's condition improved, the temperature subsided, and the febrile periods were shortened. Antibiotic therapy was discontinued, and the corticoid was gradually reduced to 0.75 mg. t.i.d. He was discharged on July 10, 1959.

The final eye visit in August, 1959, showed the right visual acuity to be 20/40, and the left to be 20/60.

He did extremely well following this, and the steroid was withdrawn. His appetite improved and his disposition became more pleasant. The chest cleared clinically but retained bilateral hilar shadows. The abdominal wound developed a stitch abscess from which *Staphylococcus aureus*, coagulase positive was cultured. He seemed to respond to erythromycin but, in spite of clinical improvement, the chest X-ray films showed progressive spreading of the pneumonitis, and nitrofurantoin was ordered. Platelets at this time had increased to 106,000, WBC 10,400 with 62-percent lymphocytes, 30-percent polymorphonuclear leukocytes, and eight-percent stabs. Cytoplasmic inclusions still were identified in the lymphocytes.

Because of shortness of breath and a fever of 103°F., he returned to the hospital on August 17, 1959, where copious amounts of pus were evacuated from the abdominal wound. He was given gamma globulin intramuscularly and blood transfusions and was discharged on September 5, 1959.

He seemed to be relatively well for one week but returned to the hospital on September 16, 1959, with a temperature of 103°F., labored respirations, and rales. Chest X-ray films showed extensive infiltrations in both lung fields. Platelets were 318,000, hematocrit 32, WBC 8,250 with 68-percent lymphocytes, 28-percent polys and three-percent stabs. There were eight nucleated RBC per 100 WBC. Inclusions were encountered in the lymphocytes. *Staphylococcus aureus*, coagulase positive, was cultured from the throat. He had a septic course and died suddenly on September 21, 1959.

FAMILY HISTORY

It is interesting to note the relationship of the parents who are cousins; both their mothers had the same mother but different fathers. There are two normal male siblings, both younger than N. W. The peripheral blood of both parents and siblings is normal.

HISTOPATHOLOGIC EXAMINATION

At autopsy, viral cultures were made from the spleen, brain, and peripheral blood and were negative. A peculiar cellular infiltration of the viscera, including the enlarged liver (1,300 gm), adrenals, pituitary, kidneys, the lungs, lymph nodes, optic nerves and choroids

was observed. Marked pulmonary edema, generalized lymphadenopathy which was most marked in the retroperitoneum, cerebral edema, perivascular infiltration by lymphocytes and histiocytes, interstitial fibrosis and edema of the myocardium were also noted.

On gross examination, both eyes showed identical changes. They were of average size and consistency, but transilluminated unusually well. The irises appeared pink, due to the absence of pigment, and the structure of the sphincter muscles was unusually well outlined. The remainder of the exterior of the eyes were not remarkable. Horizontal sections were made. All the intraocular structures were devoid of pigment except for a light brown scattering of particles which was observed on the posterior surface of the iris, ciliary body and in the choroid. The ora serrata was difficult to delineate grossly except for a fine line. The retinal vessels were difficult to trace because of the lack of choroidal pigment behind them. The macular region and the optic nervehead appeared edematous.

Microscopic examination revealed the following unusual features. The iris exhibited a remarkable decrease in pigmentation as compared to the normal "blue-eyed" iris. The anterior border layer contained only an occasional lightly pigmented melanocyte. The pigment epithelium of the iris was almost completely nonpigmented; there were, however, occasional lightly pigmented cells (fig. 1). The dilator muscle was seen unusually well.

The ciliary epithelium and choroid also exhibited the depigmented appearance observed in the iris (fig. 2). The pigment epithelium of the retina was almost completely devoid of melanin granules, and only an occasional cell showed evidence of pigmentation (fig. 3).

The optic disc was edematous (fig. 4). The retinal layers surrounding the disc were laterally displaced, and a collection of eosinophilic subretinal exudate was present be-

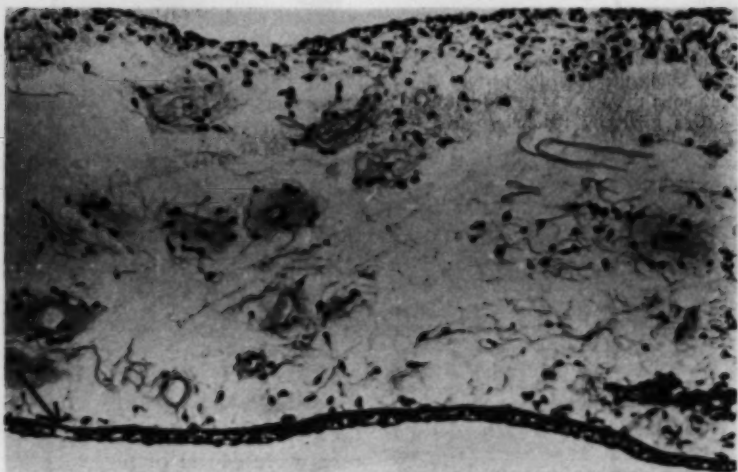


Fig. 1 (Spencer and Hogan). Iris (hematoxylin-eosin, $\times 175$). Note absence of pigment in epithelial layer. The dilator muscle (arrow) is seen unusually well.

tween the layer of rods and cones and the pigment epithelium near the disc. The central retinal vessels were patent and congested. They were surrounded by cells of the lymph-

ocytic series which grossly resembled immature lymphocytes. The perineural sheaths and neural columns of the optic nerve were infiltrated by cells similar to those observed

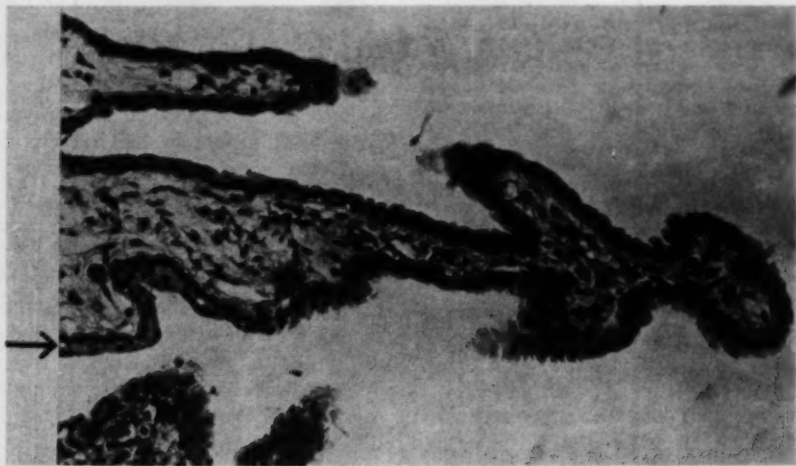


Fig. 2 (Spencer and Hogan). Ciliary processes (hematoxylin-eosin, $\times 240$), showing absence of pigment in epithelial layers (arrow).

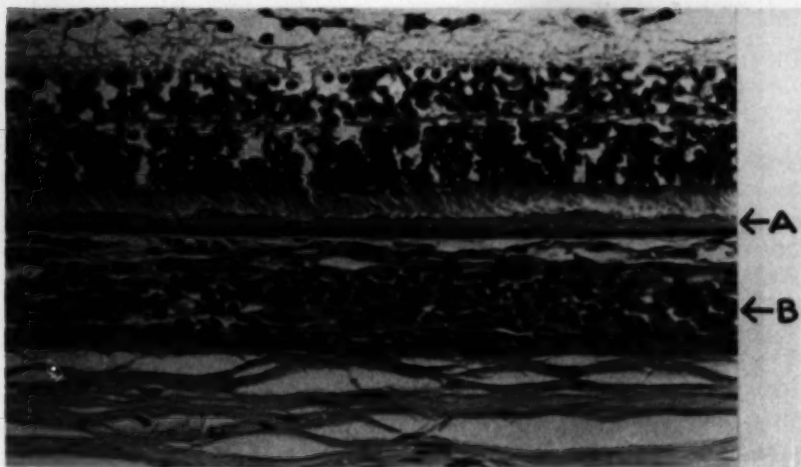


Fig. 3 (Spencer and Hogan). Retina and choroid (hematoxylin-eosin, $\times 365$). (A) Note absence of melanin granules in retinal pigment epithelium. (B) Reticulo-endothelial cells diffusely infiltrating the choroid.

surrounding the central retinal vessels. Similar cells were noted throughout the deeper layers of the choroid (fig. 5).

DISCUSSION

The presence of pigment-containing cells

in the epithelial layers of the iris and retina, as well as the stroma of the choroid, indicates that only a partial degree of albinism is present in this case. It is interesting to note that the choriocapillaris is entirely normal in appearance, and does not exhibit any evidence



Fig. 4 (Spencer and Hogan). Optic nervehead (hematoxylin-eosin, $\times 40$). Papilledema. Note lateral displacement of retina relative to the end of Bruch's membrane.

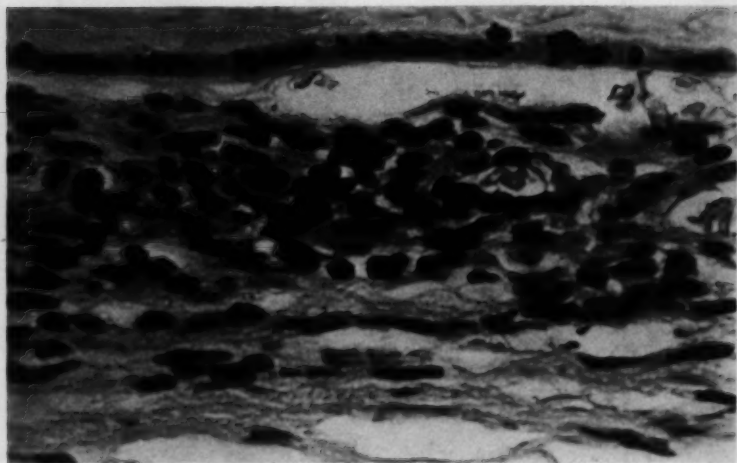


Fig. 5 (Spencer and Hogan). Choroid (hematoxylin-eosin, $\times 920$). Higher power view to show the diffuse infiltration of the choroid with round cells.

of a developmental anomaly. It has been suggested that since the pigment epithelium of the retina and the choriocapillaris appear at about the same stage of embryologic development they are dependent upon each other for their mutual development. Similar statements have been made regarding the absence of normal development of the macula in albinos.

We found no histopathologic evidence to indicate the presence of any structural abnormality in either the choriocapillaris or the macula in either eye. It is possible that these changes might occur in true albinism.

The inflammatory infiltration of the optic nerve and uveal tract associated with papilledema is unusual. The cells resemble imma-

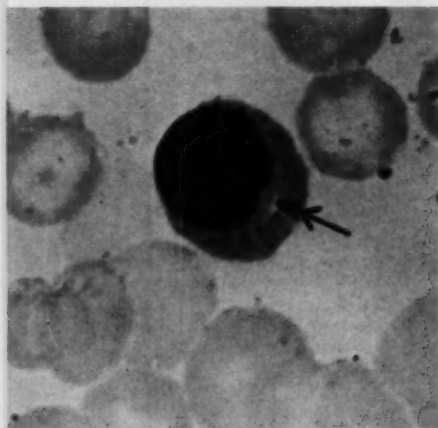


Fig. 6 (Spencer and Hogan). Peripheral blood smear (Giemsa, $\times 1,400$). Cytoplasmic "inclusions" (arrows) in mononuclear cells.

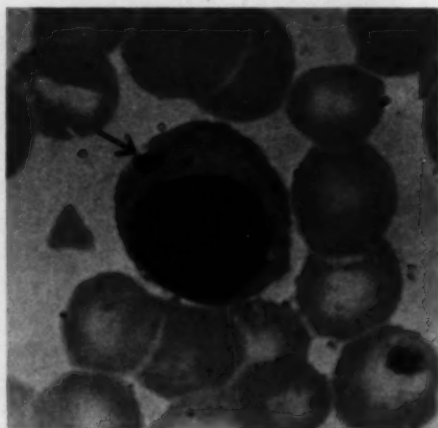


Fig. 7 (Spencer and Hogan). Peripheral blood smear (Giemsa, $\times 1,400$). Cytoplasmic "inclusions" (arrows) in mononuclear cells.

ture lymphocytes, and are similar in nature to those observed in the brain and throughout the viscera. No granulations are observed in these cells; however, smears of the peripheral blood obtained premortem exhibited leukocytic "inclusions" (figs. 6 and 7) which closely resemble those described by Chédiak and Higashi.

Donohue and Bain³ also observed this "peculiar type of 'encephalomyelitis'" and commented on the diffuse infiltration of the central nervous system with inflammatory cells. They suggest that this probably represents a reaction which is secondary to an underlying primary degeneration of the central nervous system. These cells may also be considered to represent merely the central nervous system component of a generalized reticulohistiocytic abnormality.

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WEGENER'S GRANULOMATOSIS: A CASE REPORT*

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The syndrome known as Wegener's granulomatosis, or midline lethal granuloma, has, in the past few years, been called to the attention of ophthalmologists because of the associated ocular pathology. It is more widely known in the general literature because of the general systemic manifestations. The ocular signs are quite variable and include numerous manifestations of necrotizing vascular disease. One of the more common signs,

SUMMARY

The clinical and histologic ocular findings in a typical case of Chédiak-Higashi syndrome are reported. Photophobia, partial albinism, papilledema and cellular infiltration of the choroid and optic nerve are observed in each eye. The systemic manifestations present in this case are characteristic of the disease and include hepatosplenomegaly, generalized lymphadenopathy, frequent pyogenic infections, partial albinism and hematologic abnormalities.

Department of Ophthalmology (24).

ACKNOWLEDGMENT

We wish to thank Milton Bassi, M.D., for his kindness in allowing us to obtain the eyes at autopsy and to Taylor Smith, M.D., for his help in obtaining details of the clinical and family history of the patient.

however, is marginal ulceration of the cornea which does not respond to topical antibiotics or steroids. This is a report of one such patient who had this presenting symptom and upon whom the other systemic manifestations of the disease were rather classical and led to the ultimate diagnosis.

Most of the case reports of patients with this disease have been post mortem. This report concerns a patient who has survived the disease with an intermission induced, probably, by systemic steroid therapy for almost two years.

The disease has been described by Mc-

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Donald and Edwards¹ as a triad, consisting primarily of involvement of three systems: vascular, respiratory, and renal. Pathologically it appears to be a focal necrotizing vasculitis which involves both the arteries and veins and produces necrotizing granulomas of the respiratory tract and a focal glomerulonephritis. Clinically, it is manifested by intractable rhinitis and sinusitis, nodular pulmonary lesions, and terminal uremia. The associated necrotizing marginal corneal ulcer may bring it to the attention of the ophthalmologist.

Treatment is relatively ineffective and consists in the administration of antibiotics to control secondary infections and apparently systemic steroids can, in some cases, produce remissions of a somewhat indefinite period. The etiology of the disease is unknown.

The differential diagnosis of this disease would include periarteritis nodosa, Boeck's sarcoid, fungus diseases of the chest, such as coccidiomycosis, histoplasmosis, and the more common granulomatous diseases, such as syphilis and tuberculosis.

Frayer² has recently described the histopathology of the perilimbal ulceration in Wegener's granulomatosis. Essentially the histopathologic study of this lesion reveals a necrosis of the sclera and marginal cornea, apparently resulting from occlusion of the anterior ciliary vessels by the necrotizing angiitic processes.

REPORT OF A CASE

The patient, a 47-year-old white man, was first seen in consultation on December 15, 1958, because of an inflammation of the left eye of two or three months' duration. He was referred by an otorhinolaryngologist because of headache, excessive tearing, and chronic sinusitis.

Examination at this time showed a normal right eye with vision of 20/15 and an inflamed left eye with 20/70 vision. The left eye showed an inflamed nasal conjunctiva with a small ulcer in the nine o'clock position near the limbus. There was, in addition, a line about 180 degrees nasally that showed a "furrow-type marginal degeneration." The patient was placed on Neohydrolasol solution locally and advised to return if there was no improvement.

The patient returned on January 19, 1959, without signs of improvement. He was then placed on systemic steroids. The patient was followed until

May 27, 1959, during which time the ulcer progressed and became more severe in nature, despite the use of topical chloramphenicol, as well as the systemic and topically applied steroids.

On May 27, 1959, he was admitted to St. Luke's Hospital in Denver for general systemic tests and for biopsy of the ocular lesion and the surgical construction of a conjunctival flap to cover the ulcerated area. All treatment was temporarily discontinued. The ulcerating area appeared to be near the perforating stage. Under topical anesthesia, as well as local block, the lesion of the eye was biopsied (fig. 1).

The microscopic description of the marginal ulcerated area was:

The section is partially covered by stratified squamous epithelium. Scattered through the epithelium are clusters of neutrophils, macrophages, and lymphocytes. The underlying propria is focally edematous and infiltrated by acute and chronic inflammatory cells, the latter predominating. In several minute areas the surface epithelium is absent. The section exhibits sheets of orderly stratified squamous epithelium with a small amount of underlying propria exhibiting fibroblastic proliferation and infiltrations of lymphocytes, macrophages, eosinophils, and scattered neutrophils.

The pathologic diagnosis was marginal corneal ulcer, left eye.

While in the hospital, the general findings were as follows: On admission the general examination revealed a 46-year-old white man in moderate distress. The temperature was 99°F, pulse 98, respirations 18, and blood pressure 115/75 mm.Hg. The right eye was normal and the left eye showed a necrotizing limbal ulcer covering the nasal limbus and extending, by virtue of a corneal opacity, almost to the midline (fig. 2). Examination of the throat revealed a mild granular pharyngitis. There were no cervical nodes. The thyroid was not palpable. The chest had normal excursion and was clear on auscultation and percussion. The heart was not enlarged and had a normal sinus rhythm without murmur or rubbing sounds. Examination of the abdomen revealed a palpable liver edge. The spleen and kidneys were not felt. The extremities were normal and neurologic examination was negative.

The laboratory work on admission included WBC 9,150, with 71 segs, 22 lymphocytes, three monocytes, two eosinophils, and two basophils. The sedimentation rate was 44 mm. per hour. Serology was negative. The urine examination was negative for sugar, acetone, and protein. There were a few red and white blood cells in the sediment.

The course in the hospital was: After admission the patient ran a low-grade fever and complained of occasional headaches. On June 22nd, he began to complain of severe thoracic pain located mostly in the lower left chest, increased by deep inspiration and necessitating the use of morphine for the relief of pain.

He also complained of joint pain located in the left hand. Physical examination at that time did not reveal any abnormal sounds or dullness or localized tenderness in the chest. Febrile agglutina-

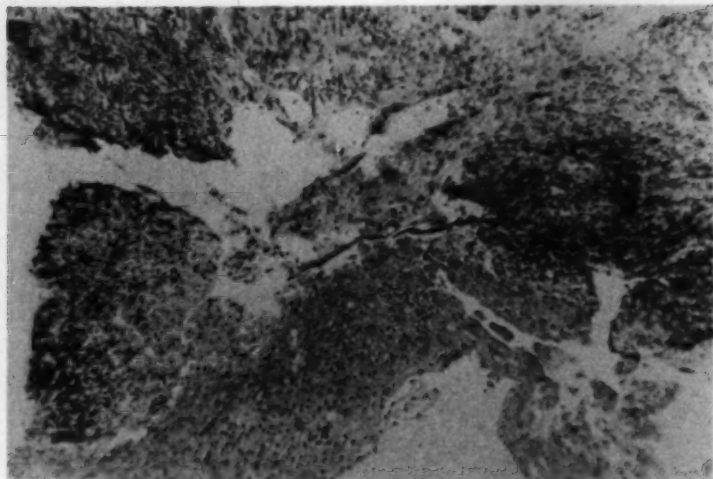


Fig. 1 (Tyner). Section from biopsy from lesion of the left eye.

tions were negative. PPD, coccidioidin, and histoplasmin skin tests were negative. A urinalysis on June 29, 1959, revealed a large increase in the number of red cells.

The electrocardiogram was normal. A chest film revealed numerous oval and rounded densities throughout both lungs. These were interpreted as possible fungus sites or possibly a widespread carcinomatosis. X-ray films of the hands revealed normal bone and joint structure. X-ray films of the upper gastro-intestinal tract showed no abnormalities. A bone-marrow examination was normal. On June 24th, a bronchoscopy was performed and bronchial washings taken, which were negative.

The patient continued to have severe chest pain, loss of weight, general malaise, symptoms of sinu-

itis and arthralgia. He demonstrated a progressive downhill course.

An exploratory thoracotomy was performed on June 29, 1959. Examination of the right lung showed granulomatous lesions throughout, with extensive focal necrosis. A right upper lobectomy was done, as well as a biopsy of the right hilar node. Gross sections of the lung are exhibited in Figures 3 and 4, and the pathologic sections of the lung in Figure 5.

The pathologic diagnosis of the lung specimen was:

Gross description. A frozen section shows a specimen consisting of the right upper lobe of a lung measuring 17 by 14 by 4.0 cm. The mottled purple gray-pink pleura is smooth. There are several nodular firm masses on palpation, up to 4.0 cm. in diameter. Cut surfaces are moist dark red with scattered elevated granular mottled red tan

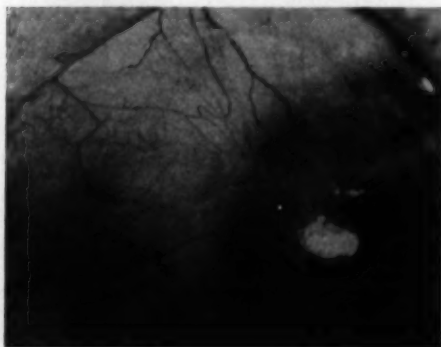


Fig. 2 (Tyner). The left eye on January 6, 1960, showing conjunctival flap.

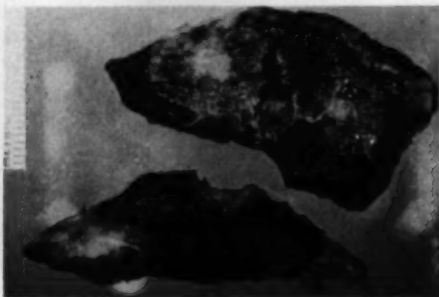


Fig. 3 (Tyner). Gross sections of the lung

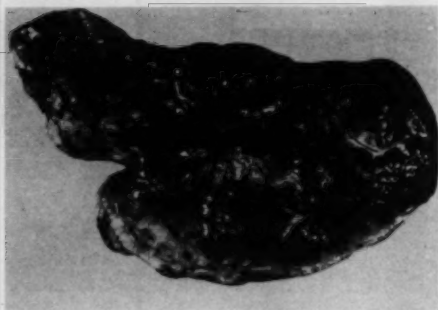


Fig. 4 (Tyner). Gross section of the lung.

yellow areas, up to 2.5 cm. in greatest diameter.

Microscopic description. Sections of the poorly defined lung nodules exhibit extensive areas in which alveoli are largely obliterated by marked fibroblastic proliferation. These areas contain prominent focal infiltrations of macrophages, lymphocytes, eosinophils, plasma cells, and scattered neutrophils. Macrophages frequently contain hemosiderin pigment. The areas of inflammation are in many instances small ovoid foci approaching abscess formation in their appearance.

Scattered through the granulomatous areas are alveolarlike spaces lined by plump cuboidal cells. In rare instances there are singly occurring or small clusters of multinucleated giant cells. Toward the periphery of the nodules alveolar architecture is apparent. The alveolar septa are thickened and infiltrated by acute and chronic inflammatory cells.

The alveolar spaces frequently contain fresh blood or partially organized, deeply eosinophilic fibrinous material.

In rare instances, there are small vessels, apparently arteries, exhibiting marked focal infiltration of the entire vessel wall by acute and inflammatory cells, the former predominating. Medial necrosis is not apparent. These vascular lesions are quite rare, the granulomatous process far overshadowing the vascular lesions.

Bronchial walls are quite diffusely and heavily infiltrated by acute and chronic inflammatory cells, the latter predominating. Peribronchial lymph nodes exhibit moderate reticulo-endothelial hyperplasia and moderate anthracotic pigmentation.

From this specimen a diagnosis of Wegener's granulomatosis of the right upper lobe of the lung was made.

Following the lobectomy, the patient was placed on rather high doses of systemic steroids. In addition, he was placed on systemic antibiotics and topical steroids. Under the influence of the steroids, given in fairly high doses, the patient became relatively asymptomatic and was discharged from the hospital on July 8, 1959.

The conjunctival flap over the ulcerated area gradually became retracted over a follow-up period extending to January 6, 1960. The visual acuity returned to 20/40 in the affected eye. The patient has been able to resume his occupation as a farmer and, despite manifestations of steroid therapy, such as moon face and weight gain, has been reasonably comfortable. He, in addition to these symptoms, developed a duodenal ulcer which has responded to medical therapy and at the present time is being maintained on Medrol (4.0 mg., four times daily).

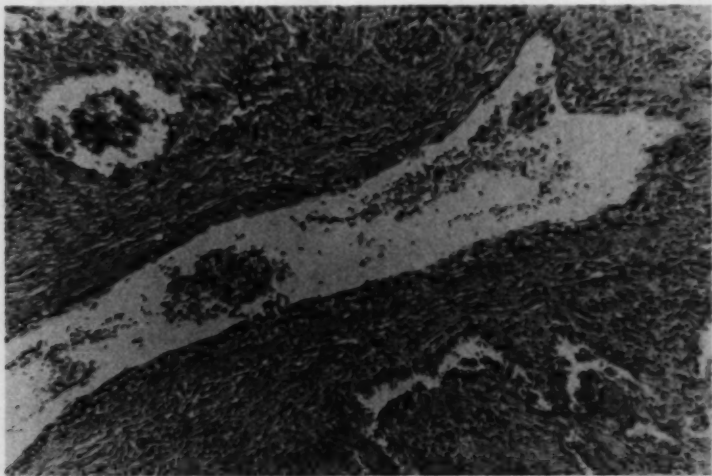


Fig. 5 (Tyner). Section, demonstrating the microscopic pathology of the lung.

SUMMARY

The clinical course of a patient with a marginal corneal ulcer and systemic manifestations of Wegener's granulomatosis, including nasopharyngeal symptoms, pulmonary distress, joint pain, and glomerulonephritis¹ as manifested by rather marked hematuria is reported. A biopsy report of the ocular lesion, as well as a gross and microscopic description of the right upper lobe biopsy, are reported. The patient has undergone a prolonged remission under the influence of systemically administered steroids.

The value of the conjunctival flap in promoting healing of the corneal ulcer and pre-

vention of perforation is debatable. It is considered likely that the remission of the ocular signs and symptoms is based primarily on the use of the systemic steroids. The importance of recognizing this disease syndrome is emphasized because of its ultimate lethal characteristics due to the accompanying systemic disease.

324 Metropolitan Building (2).

ACKNOWLEDGMENT

I am indebted to Dr. William D. Millett, Department of Pathology, St. Luke's Hospital, Denver, Colorado, for the pathologic information included in this report in the diagnosis of this patient's disease. In addition, he is indebted to Dr. Charles DeMong, Denver, Colorado, for the lung biopsy which led to the diagnosis of the patient's disease.

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SOME DETAILS OF THE TECHNIQUE OF CYCLODIALYSIS*

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Among the antiglaucomatous operations, cyclodialysis is unique in its surgical rationale as well as in its multifaceted history. It is the only operation aiming at a communication between the anterior chamber and the suprachoroidal space, and there is probably no other procedure so highly praised by some at some times and so thoroughly condemned by others at other times.

SCOPE AND MODE OF ACTION

Since Heine published his glaucoma operation 55 years ago, he and many other ophthalmologists have used this procedure for different types of glaucoma. The first experiences were gathered on eyes suffering from

absolute glaucoma. Soon it became obvious that Heine's operation was more efficient in chronic simple than in congestive cases, to use the nomenclature of that time (fig. 1).

Extensive studies about the technique, indications, complications, and end-results of cyclodialysis were published from Elschnig's clinic by Waldstein in 1910, by Salus in 1920, and by Stein in 1930 and from Budapest by von Grosz.

In this country, Gradle²² became one of the early advocates of cyclodialysis.

The rationale of the operation was to obtain a cleft between uveal tissue on one side and the outer coat of the eyeball on the other, substituting for the physiologic aqueous humor elimination, so that the aqueous humor might seep into the suprachoroidal space and be absorbed there. Elschnig¹⁸ was the first to prove histologically that this com-

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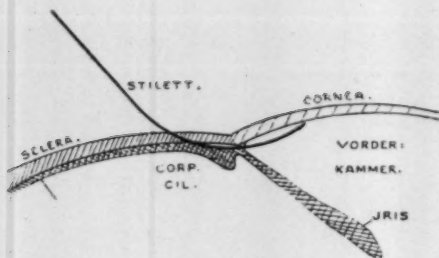


Fig. 1 (Ascher). Separation of ciliary body and iris root as shown in original sketch by L. Heine, 1905. Curvature of spatula (Stilett) shows possibility of injuring corneal endothelium and Descemet's membrane.

munication could actually be established: In an eye normalized by cyclodialysis for 14 years he found histologically an open connection between anterior chamber and suprachoroidal space at the site of the operation. Barkan, Boyle, and Maisler,⁷ from a gonioscopic study of 14 glaucomatous eyes, concluded that the eye pressure was normalized only in those eyes in which the surgical cleft was gonioscopically visible. Also Sugar found an "all or none" relationship between success of this operation and a gonioscopically visible cleft.³⁸ Viikari and Tuovinen,⁴² however, found that sometimes the tension was normalized without a visible cleft and that the presence of a cleft did not guarantee normal tension. The older opinion expressed by Salus³⁵ and by others that the mode of action of cyclodialysis is based on traumatic damage to the ciliary body found some support from studies of the fluid elimination after this operation (Goldmann,²¹ Kronfeld³⁰). Barkan,⁶ as well as Vannas and Bjoerkenheim,⁴¹ found histologically proved ciliary body atrophy following cyclodialysis.

About 17 years ago I found that glaucomatous eyes normalized by medication or surgery more often showed clear aqueous veins than before treatment and that in aqueous veins which, before treatment or surgery, showed blood influx phenomena, aqueous influx phenomena appeared after surgery or successful treatment, indicating a

more vigorous aqueous humor elimination. Thomassen³⁹ and later investigators like Goldmann²¹ confirmed these observations. If, however, glaucoma operations resulted in hypotony, fewer or no aqueous veins were found. This was first reported by Mathieu,³¹ François,¹⁹ and L. and R. Weekers⁴⁴ on eyes subjected to iridencleisis. Similarly, Goldmann saw disappearance of aqueous veins after cyclodialysis. The question arose whether the aqueous veins of hypotonic eyes become invisible due to markedly reduced production of aqueous humor and lowering of the intraocular pressure below that prevailing in the episcleral veins, or because the aqueous humor elimination after surgery is deviated into the newly formed artificial channels. A third explanation could be that the aqueous veins become indiscernible due to lack of red blood cells.

On rabbit eyes, Binder and Binder⁸ proved that the aqueous veins do not become obliterated after cyclodialysis: Eight to 10 months after the operation they injected fluorescein into the anterior chamber and the dye appeared in the aqueous veins. This, of course, is not necessarily valid for human glaucomatous eyes.

Together with Saeteren,³⁴ Thomassen mapped the aqueous veins of glaucomatous eyes photographically before and after cyclodialysis at intervals varying between 11 and 16 months. Since there was no difference in the appearance of aqueous veins before and after surgery and all eyes had normal pressure at the time of the postoperative mapping, the authors concluded that the resistance to aqueous humor elimination must have been lowered while the production of aqueous humor must have remained unchanged. To Goldmann's statement²¹ that the aqueous veins disappeared after cyclodialysis Saeteren and Thomassen objected because he had not ascertained the site and number of aqueous veins before surgery, had examined some of the eyes very early after surgery, and some of the eyes studied were definitely hypotonic.

INDICATIONS

Spaeth³⁶ considered cyclodialysis a very satisfactory procedure for simple noninflammatory glaucomas in the lower pressure ranges and in glaucoma secondary to cataract extraction, while Wiener and Scheie⁴⁵ recommended it as a primary operation for aphakic glaucoma, and as a secondary operation for narrow-angle glaucoma after unsuccessful iridencleisis, and wide-angle glaucoma after failure of filtering procedures. Increasing recognition seems to be given this operation as an excellent procedure for open-angle and secondary glaucomas with base pressure between 30 and 40 mm. Hg (Reese³³), with recent interpretation of tonometer readings some 5.0 or 6.0 mm. lower. Haisten and Guyton²⁶ recently reported good results of cyclodialysis in eyes with wide-angle glaucoma.

Numerous modifications were proposed concerning minor details as location of the incision, instruments, suturing of the wound or direction of the sweep.⁹ Dissatisfied with late results, some authors suggested to combine cyclodialysis with trephination, with iridectomy or both^{20,46} or with introduction of magnesium metal into the newly formed channel.⁴⁰ Chandler¹¹ favors cyclodialysis combined with iridectomy for eyes suffering from neglected narrow-angle glaucoma irrespective of whether the intraocular pressure is 30 or 70 mm. Hg.

Since in many cases the choice of the proper procedure may be difficult I want to mention a suggestion recently made by Kleinert.²⁸ He used visualization of aqueous veins by fluorescein injection into the anterior chamber: If fluorescein filling revealed the presence of numerous aqueous veins he decided for cyclodialysis; if the injection proved paucity of aqueous veins he chose fistulization (fig. 2).

This way of thinking seems to be supported by Grant's observation²³ that, in enucleated human eyes, cyclodialysis without opening the trabecular meshwork does not

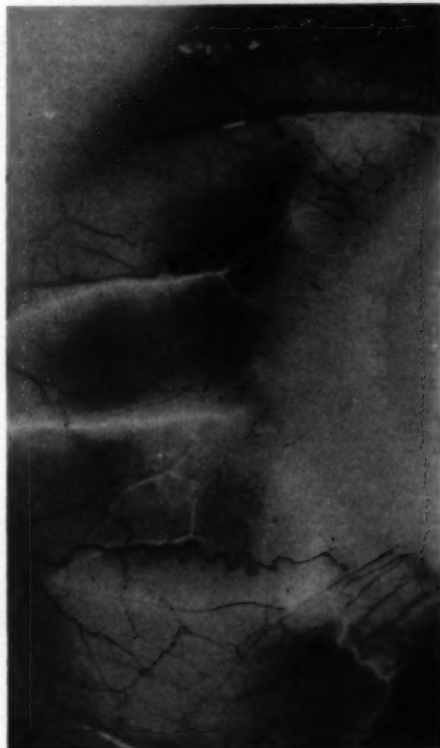


Fig. 2 (Ascher). Visualization of aqueous veins by fluorescein injection into the anterior chamber. (Courtesy of Dr. H. W. Kleinert, 1958; not previously published.) Stained are the anterior chamber and the aqueous veins, the pupil shining darker.

appreciably increase the facility of aqueous outflow. Recently, Dellaporta used a slightly modified cyclodialysis spatula to separate experimentally the trabeculae from the scleral spur, a procedure aiming at improvement of the drainage via the canal of Schlemm but at the same time separating a small area of the ciliary body from its attachment to the outer coat of the eye.¹³⁻¹⁵

I do not plan to discuss or even to enumerate all suggestions for improvement of cyclodialysis but shall dwell on the technical difficulties encountered during the procedure, on measures to overcome them and to avoid complications during the operation and in the postoperative course.

In my experience, cyclodialysis is not only useful as a first surgical step, but sometimes is surprisingly efficient on eyes subjected to repeated surgery without satisfactory result, and in secondary glaucoma after perforating injury to the anterior segment. In eyes of Negroes, it seems to be more successful than other antiglaucomatous procedures.

TECHNIQUE

The following technique of cyclodialysis was developed by Elschnig between 1907 and 1930 and in detail described by Salus³⁵ and by Stein.³⁷ The preferred location for the operation was the temporal lower quadrant but the operation may be repeated if necessary in any other quadrant between two recti muscles. One-half cc. of a solution of cocaine, adrenaline, and pilocarpine was injected subconjunctivally, then the eyeball was massaged over the closed lids, a procedure which Elschnig had used and advocated for many years to enhance the anesthesia and to lower the intraocular pressure before cataract and glaucoma operations. The conjunctiva was incised parallel to and about 10 mm. from the limbus. The sclera was denuded, the exposed episcleral vessels were severed, and bleeding was stopped by careful sponging. Then the sclera was grasped with a sharp-tooth forceps and incised with a small-bellied scalpel between forceps and limbus, about five mm. from the latter. The distance of the incision from the limbus should be slightly greater in myopic eyes.

There seems to be some misunderstanding as to the shape of Elschnig's cyclodialysis spatula. Some illustrations show this instrument with a definite concave or convex curvature of the operative tip. Contrariwise, from the straight handle, the very slightly curved

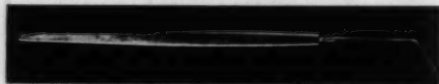


Fig. 3 (Ascher). Cyclodialysis spatula as recommended by A. Elschnig (about one-half actual size). See text for description.

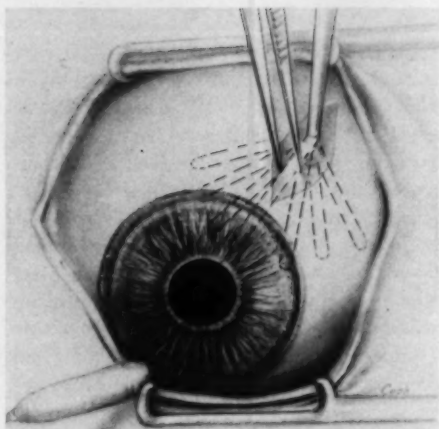


Fig. 4 (Ascher). Prevention of hemorrhage during cyclodialysis according to A. Elschnig. See text for detailed description. This drawing also shows successive thrusts of the spatula, as later suggested by Ascher.

end should project at an angle of about 130 degrees, the operative part should be about one and one-half mm. wide, not more than one-third mm. thick, smooth along its edges and well rounded at the tip (fig. 3).

Elschnig recommended to sweep the spatula 90 degrees in each direction to make the full excursion at least 180 degrees so that in its two final positions the operative end of the spatula would stand parallel to the limbus. To prevent hemorrhage into the chamber the assistant had to exert pressure with a small cotton applicator on the sclera opposite to the incision. The cotton applicator remained in its position during suturing of the conjunctiva and during application of the eyepad which the surgeon pressed against the lids while taping (fig. 4). The dressing was kept in place with slight pressure for 24 hours. The eye was inspected the following day and one-percent homatropine instilled to prevent formation of synechias. At further dressings, mydriatics or miotics were used as indicated.

RESULTS

The early experiences of the Prague Eye Clinic were reported by Elschnig,¹⁶⁻¹⁸ Wald-

stein,⁴³ Kraupa,²⁹ and in very comprehensive articles by Salus³⁵ and by Stein.³⁷ Salus reported in a group of 200 compensated glaucomas 157 successes concerning tension, visual acuity, and visual field. Of these 157 patients, 60 were followed for more than six months, 27 for more than two years, two for nine and one-half years. Of 150 uncompensated cases, 95 had good results: 33 cases for more than six months; 17 cases for over two years. Later statistics from the Prague Clinic gave somewhat better results due to improvement of the technique and better selection of eyes to be operated upon.

In 348 eyes from the Prague Eye Clinic, Stein³⁷ found a greater percentage of good results in what Elschnig called compensated glaucoma, corresponding approximately to open-angle glaucoma. Decompensated, that is, angle-closure glaucoma, responded better to iridectomy or fistulizing operations. Similarly, von Grosz in his large material of more than 4,800 eyes figured 75-percent good late results of cyclodialysis in simple glaucoma and only 55 percent in congestive glaucoma.

COMPLICATIONS

The most common complication of cyclodialysis is hemorrhage into the anterior chamber (60 percent of 348 in Stein's series; in a more recent Helsinki⁴² study, 63 percent of 290 operations). Bleeding is undesirable because of the possibility of organization in the area of the artificial cleft with permanent closure of the latter; larger hemorrhages obstruct visibility during the operation, may prolong the patient's stay in the hospital and encourage formation of synechias. By introduction of a narrow Daviel spoon into the chamber and mild pressure on the cornea most of the blood can be evacuated during the operation. Elschnig's technique to prevent bleeding has been mentioned.

A very common but less serious complication during cyclodialysis is peeling of Descemet's membrane; in many cases, curled glassy filaments or membranes can be seen

on the corneal microscope weeks and years after the operation. In Stein's series³⁷ this complication occurred in more than 50 percent but rarely is this injury as extensive as to cause corneal edema. To avoid this complication a graduated spatula was suggested, but well-maintained instruments and careful instrumentation should suffice to prevent corneal damage.

More dangerous but fortunately less common is iridodialysis which occurred in six percent of the operations. Improper scleral incision or rough handling of the spatula may lead to perforation of the choroid and presentation of vitreous body (three percent in Stein's series). Means to avoid these complications will be described.

Among the postoperative complications, mild iritis is very common (33 percent in Stein's cases) and is to be treated with postoperative mydriatics. Severe iritis is rarely seen and requires intensive treatment. With fever therapy and steroids we are better prepared to combat this dangerous complication.

In 10 percent of Stein's patients, changes of refraction were observed, more often an increase in myopia than the opposite. Progressive loss of visual fields despite normalization of intraocular pressure occurred in 1.2 percent; it may be simulated by lens opacities¹² which may increase after cyclodialysis as after other pressure-reducing operations. Cataract formation progresses slowly (five percent in Stein's cases), seldom rapidly (one-half percent).

After 605 operations Salus³⁵ found that the eye pressure rose immediately if aqueous humor did not escape. If aqueous was lost, the eye pressure rose a few hours later. In either series the pressure increase lasted for one to three days, rarely a week or more. Permanent postoperative eye pressure increase is an exception, apparently restricted to narrow-angle cases which should not be subjected to cyclodialysis anyway.

Since the effect of cyclodialysis can be approximately graduated by making the separated sector proportional to the intraocular

pressure, overdosage resulting in severe hypotony should not occur as it occasionally does after fistulizing procedures. It seems now possible to prevent hypotony by scleral diathermy coagulation along the borders of the area to be detached.¹⁰

TECHNICAL DETAILS

The following suggestions are offered to make the operation easier to perform, less injurious, and more efficient. There is no claim of originality for all of them, although I might have used and mentioned one or the other before they were published elsewhere.

Since pupillary dilatation is not desirable, cocaine should be avoided. Butyn instillation and subconjunctival or retrobulbar injection of procaine will guarantee a painless procedure. Preoperative pilocarpine instillation is mandatory. Diamox or hyperosmotic intravenous injections may be indicated before surgery in eyes with irreducibly high pressure.

To avoid collection of blood in the pocket between sclera and ciliary body cyclodialysis should be performed in the upper half of the eyeball, preferably in the temporal upper quadrant and not, as Heine²⁷ and many subsequent authors suggested, in the temporal lower quadrant. If repetition of the procedure becomes necessary, the nasal upper quadrant can be attacked. There is another advantage to this location: Gravity may help to keep the newly formed gap open since the lens is specifically heavier than the aqueous humor and thus will, through its suspensory zonula, exert some traction on the ciliary body. As a proof of this concept, Viikari and Tuovinen⁴² stated that the percentage of successes was higher in eyes in which the operation was performed in the upper quadrants. Haas²⁸ suggested to locate cyclodialysis in an inferior quadrant if it follows an iris inclusion operation so that the upward traction of the iris may help to keep the surgical gap open. The proposed rule to locate cyclodialysis according to the gonioscopic findings sounds promising but should, in my opinion,

be restricted to the avoidance of this operation in eyes with primary narrow-angle glaucoma.

After incision of the conjunctiva and freeing of the scleral surface, the sclera should be grasped firmly with a fine-tooth forceps between the intended scleral incision and the limbus. With the forceps, the sclera is pulled slightly forward and a small scalpel or Bard-Parker knife should cut the sclera at an angle of about 45 degrees which will make the introduction of the spatula very easy (figs. 5, 6, and 7).

Most surgeons seem to cut the sclera at an angle of 90 degrees which necessitates the introduction of the spatula—like a tear-sac probe—in two directions, first toward the choroid and then around the anterior scleral wound-lip, as a pivotal point, toward the chamber angle. This maneuver is more complicated and dangerous than the introduction of the spatula after a 45-degree incision.

On the other hand, the successive slight strokes should be performed as suggested by Elschmig,¹⁷ Salus,³³ Spaeth,³⁶ and by others, that is, the incision should be deepened slowly until a lack of resistance indicates that the sclera has been perforated. In former publications one can find the remark that a slight sigh of the patient may mark this moment. This sigh, in my opinion, indicates insufficient anesthesia.

Slight pull on the sclera will raise it to form an almost imperceptible fold and thus prevent injury to choroid and vitreous body.³ The spatula should be introduced parallel to, and gliding along, the inner scleral surface; moving both hands toward each other, the surgeon gently pushes the spatula against the pectinate ligament and gently moves the eyeball against the spatula. Only a properly inserted and manipulated forceps can achieve this. When the tip of the spatula appears in the anterior chamber, the surgeon's hands draw apart without removing the spatula completely from the wound.

The next thrust is made very near the first, slightly nasally or temporally from it

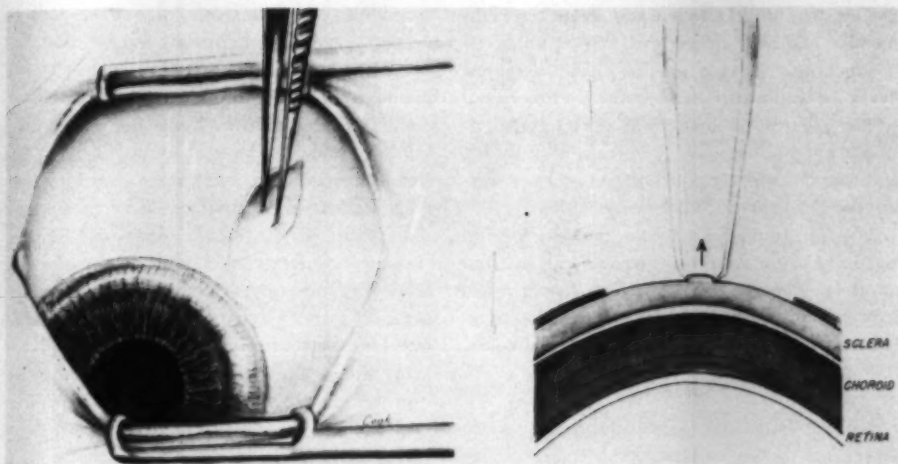


Fig. 5 (Ascher). Incision of conjunctiva in temporal upper quadrant and grasping of the sclera. An almost imperceptible scleral fold (here exaggerated) is raised in order to protect the choroid.

(fig. 4). Further thrusts follow, without sweeping, at increasingly greater angles from the first thrust until the two extreme thrusts are made 180 degrees from each other.

This modification of the procedure makes the separation of the ciliary body very easy and prevents piercing or folding of the iris; injury to Descemet's membrane and hemorrhages are less probable than with sweeping of the spatula, whether this movement be made from the incision toward the chamber

angle or from the chamber angle toward the ciliary body.

The drawing in Figure 4 should not be misunderstood in the sense that, between the thrusts, unseparated areas have to remain untouched; at the end of the procedure, the whole area should have been covered by multiple thrusts closely neighboring each other. I have used and shown this multiple thrust method for about 30 years and was

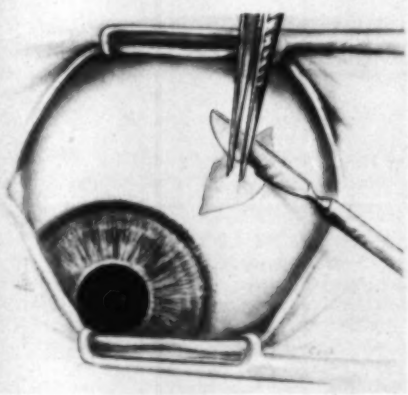


Fig. 6 (Ascher). Incision of sclera at an angle of 45 degrees facilitates introduction of the spatula.

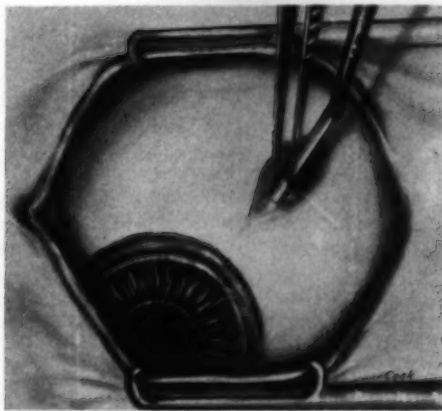


Fig. 7 (Ascher). Cyclodialysis spatula enters easily in apposition to sclera. It is not swept, but withdrawn and reintroduced at different angles.

glad to find that O'Brien and Weih³² recommended a similar procedure. (See Figure 4.)

Elschnig's advice to have the assistant press an applicator against the limbus opposite to the site of surgery is very helpful. A small air bubble may be injected into the anterior chamber if aqueous has escaped during the procedure.

The question whether postoperative steroid administration, local or systemic, can prevent or at least delay the closure of the surgical gap should be answered by statistical evaluation of a large series of well-observed cases.

SUMMARY

With the described modifications, cyclodialysis is a safe and not disfiguring operation for relief of open-angle glaucoma and glaucoma secondary to cataract operation;

sometimes it will even give good results where preceding operations have failed.

Cyclodialysis is indicated in early cases of primary open-angle glaucoma and of secondary glaucoma which do not respond to miotics and carbonic-anhydrase inhibitors and for eyes which previous glaucoma surgery failed to normalize. For the proper indication all diagnostic aids—ophthalmoscopy, tonometry, field studies, provocative tests, gonioscopy, and tonography—are needed. Particularly, young patients should be able to continue an active normal life after this operation, while frequent instillation of miotics may disable an otherwise healthy person. Most of the complications of cyclodialysis can be avoided by adhering to meticulous observation of the technique.

5 West Fourth Street (2).

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FOCAL IONIZING RADIATION OF THE POSTERIOR OCULAR SEGMENT*

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Most data concerning the effects of focal ionizing irradiation on the posterior ocular segment have been derived from experience

treating intraocular malignancy by means of locally applied radium, radon seeds and, more recently, the artificially produced isotopes cobalt⁶⁰ and tantalum¹⁸². Stallard,¹ in the 1951 William McKenzie Memorial Lecture, reviewed much of the early literature concerning the topic and Desjardins,^{2,3} 1931 review covers much of the general experience related to radiation effects upon the eye. Generally, because the physical factors relating to the energy of the radiation are incomplete, most

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early studies are solely of historical interest.

From 1934-1948 Stallard treated 15 cases of retinoblastoma, using radon seeds set in a stent which was sutured to the sclera over the tumor. Since 1948, a new type of applicator has been used. It consists of a stainless steel disc, held in apposition to the eye by means of a clip sutured to the sclera, which contains either radium or cobalt⁶⁰ as the radioactive source. Williams² has reported the experience with this applicator and Stallard³ gave additional data in the 1954 Charles May Memorial Lecture.

Cobalt⁶⁰ is used with an activity of 0.63 and 1.46 mc. for discs of 5.0 and 10 mm. respectively. The dosage is planned so as to deliver 3,500 r in one week to the surface of the neoplasm, the height of which is judged to be seven-tenths of its diameter. Radium is used in a concentration of 1.0 mg. in a disc 5.0 mm. in diameter and 2.7 mg. in one 10 mm. in diameter. The disc is removed one week after insertion.

Lederman and Sinclair⁴ have used tantalum wire sealed in polyethylene tubing in the shape of a ring and sutured to the sclera in the therapy of retinoblastoma. Four cases have been treated but details are lacking. The half-life of tantalum¹⁸² is 111 days, which would necessitate using low activity or removing the metal at some time after insertion.

The use of radium needles inserted into the orbit and the application of a Columbia paste plaque containing radium needles in the treatment of retinoblastoma has usually been disastrous.

The effects of ionizing radiation applied to the entire eye rather than to a localized area have been the subject of a number of studies since Chaluppeky⁵ exposed the right eye of rabbits to an X-ray beam in 1897, less than a year after Roentgen's description. Cibis and his co-workers⁶ have described in detail the effects of acute ionizing radiation injury to the retina. An acute dose of 2,000 r of X-radiation was sufficient to impair or abolish the electroretinogram and to cause pyknosis

and autolysis of the rod nuclei, followed by degeneration of the outer retinal layers.

Kent and Swanson⁷ demonstrated that an acute dose of 6,000 r of X-radiation caused a decrease in retinal succinic dehydrogenase activity and an increase in glycogen, particularly in the outer retinal layers. The effects of ionization of the posterior ocular segment are similar, irrespective of the source of the radiant energy.

Newell, Harper, and Köistenen⁸ have described the effects of yttrium⁹⁰ seeds upon the posterior ocular segment, this being the only report concerning the posterior ocular effects of an isotope emitting beta rays solely. In the activity used there was marked damage to the sclera, choroid, and retina but there was no attempt to quantitate the tissue effects with the amount of radiation.

In the present study, polyethylene envelopes, as described by Newell and Harper,⁹ were attached to the sclera of rabbits. The envelopes were then filled with radioactive iodine of different activities in the different animals. The effects of this radiation were studied ophthalmoscopically and histologically at various intervals after the implantation.

TECHNIQUE

Male pigmented and albino rabbits weighing between 2.5 and 3.0 kg. were used. The animals were anesthetized with intravenous pentobarbital and ocular instillation of tetracaine hydrochloride. The eye was rotated superiorly and a conjunctival incision was made near the inferior limbus (fig. 1). The inferior rectus and inferior oblique muscles, which insert near to each other, were severed at their insertions and the sclera exposed. The polyethylene envelope was sutured to the globe at about the equator and the muscles reattached at their insertions. A pursestring catgut suture was passed through the conjunctiva but not tied. The envelope was then filled with the previously prepared radioactive solution and the excess tubing excised by means of a heated hemostat. The pursestring suture was drawn up and tied.

The immediate inflammatory reaction was minimal. The localization of the radioactive iodine in the envelope was confirmed by the absence of radiation from the thyroid gland region as measured by a Geiger-Mueller probe. Ophthalmoscopic study was made at weekly intervals after pupillary dilation with Neosynephrine until the animal was killed. The fellow eye was not treated.

The dosage factors used in animal studies are shown in Table 1. Figure 2 indicates the calculated dosage at various distances from a 1.0 cm.² applicator assuming complete decay, inverse square attenuation, no absorption, and a gamma radiation level of 2.18 r/mc./hr. at 1.0 cm. Rabbits were killed at intervals varying from one week to 58 weeks after implantation in the dosage range from 0.18 mc./cm.² to 1.5 mc./cm.². In the range of 2.0 mc./cm.² animals were studied at intervals of 1, 2, 3, 6, 12, 22 and 26 weeks after implantation.

The iodine usually must be concentrated prior to use for focal irradiation. A volume of 5.0 to 10 ml. of I¹³¹ which has an activity of about 20 percent in excess of that required is placed in a conical centrifuge tube. To it is added 2.0 mg. of potassium iodide as a car-



Fig. 1 (Newell, Choi, Book, Harper and Simkus). Method of applying the envelope to the sclera. A human eye is depicted.

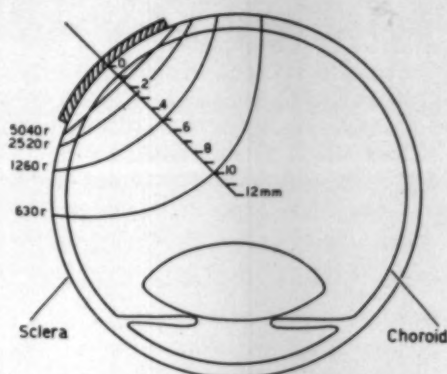


Fig. 2 (Newell, Choi, Book, Harper and Simkus). Calculated isodose curves showing gamma ray dosage surrounding a 1.0 cm.² plane applicator containing 1.0 mc. iodine¹³¹, assuming complete decay, inverse square attenuation, and no absorption.

rier. The iodine is then precipitated as silver iodide with a 50-percent excess of silver nitrate. The solution is acidified with 10-percent nitric acid, digested for one hour at 70°C. and then centrifuged. The supernatant is decanted and the precipitated silver iodide is dried with a stream of air in the dark at room temperature. The centrifuge tube containing the isotope is handled at all times in a lead-shielded container to minimize exposure.

The silver iodide is prepared for placement in the implant by dissolving it in a sufficient volume of saturated potassium iodide to yield the desired number of milluries per unit volume.

TABLE 1
DOSAGE FACTORS USED IN ANIMAL STUDIES
(Area blotter = 0.28 cm.²)

Dosage I ¹³¹ (mc.)	Isotope Density (mc./cm. ²)	Gamma-Radi- ation Dosage* (1.0 cm. from source) (r)	Mg. Hr. Radium Equivalent
0.05	0.18	113	13
0.18	0.64	403	26
0.28	1.0	630	72
0.42	1.5	945	108
0.56	2.0	1260	144

* Dosage is calculated for a mean life of 280 hr.

To fill the implant, approximately 50 cm. of polyethylene tubing (PE-10 Clay-Adams), which has been calibrated earlier, is placed in a lead container with the free ends outside. To one end is attached a syringe and the tubing is entirely filled with elemental mercury. A small quantity of nonradioactive potassium iodide is then drawn into the tubing. The tubing is then placed in the radioactive solution and a volume of 0.01 ml. is withdrawn. The portion of the tubing which has been dipped in the solution is usually markedly radioactive and is cut off and discarded. Using gloved hands, a one-inch-long 27-gauge needle with the hub removed is insinuated into the tubing for delivery of the radioactive solution to the tubing within the envelope.

A number of problems arose in making satisfactory polyethylene envelopes. Those first used were evacuated and heat sealed and the vacuum caused filling of the envelope when connected with the tubing containing the I^{131} . Failure to seal the envelope adequately, or puncture of the envelope with a surgical instrument, led to wetting of the contained blotter with body fluids and irregular distribution of the isotope. Additionally a break in the envelope would permit the isotope to be distributed to body fluids. (Because of this possibility patients are routinely administered sodium iodide intravenously

prior to filling of the envelope, to block the thyroid gland from the radioactive iodine.)

At present, polyethylene envelopes (fig. 3) are made by means of an aluminum mold at 250°F. by the machine shop at Argonne Cancer Research Hospital. Prior to sealing, a 6.0 mm. circular disc of eight-ply cellulose blotting material is enclosed in the envelope. It was found that 0.01 cc. of fluid completely saturates the blotting paper. The envelope is filled by means of a fine No. 10 polyethylene tubing (Clay-Adams) and, when the envelope is filled, the implant is sealed, using a curved hemostat with flat surfaces heated to 300°F.

A variety of blotting materials have been used. The material used in these studies was cellulose distributed under the trade-name "S-Wipe's" and manufactured by the General Cellulose Company, Inc., of Garwood, New Jersey. Eight thicknesses were used and when wet these measured 0.5 mm. in thickness. Generally speaking, the selection of the blotting paper is not too critical except that, if the blotting paper is too thick, considerable changes in the geometry of the radiation field are introduced. If the solution does not wet the entire blotting paper, the distribution will be irregular and the isodose curve distorted. It is thus desirable that the volume of fluid used completely saturates the blotting paper so as to make the radiation as uniform as possible.

Polyethylene is a generic term given to a variety of products derived when ethylene is subjected to extremely high pressure. These compounds vary considerably in their reactivity to radiation and chemicals. To ensure safety the polyethylene used was tested for reactivity in the anterior chamber of a rabbit eye. No tissue reaction was evident nine months after implantation. The material currently being used is polyethylene sheeting 0.04 mm. in thickness.

RESULTS

Ophthalmoscopic changes were noted consistently only in animals in which the isotope



Fig. 3 (Newell, Choi, Book, Harper and Simkus). Polyethylene envelope with enclosed 6.0 mm. circular disc of absorbent material. After filling with iodine¹³¹, the tubing is cut off with a heated clamp which seals the envelope.

density was 1.5 mc./cm.^2 or more. This dosage corresponded to 945-1260 r in air 1.0 cm. from the source and to 108-144 mg./hr.² radium equivalent.

In animals receiving 2.0 mc./cm.^2 , initial ophthalmoscopic changes of an ill-defined grayish-white elevation over the site of implantation were noted at examination two and three weeks after the procedure. These lesions developed into well-defined, sharply circumscribed and slightly elevated whitish areas over which were scattered numerous dark-brown pigmented dots (fig. 4). In the periphery of the area, choroidal blood vessels were evident. No hemorrhages were noted at any time.

The ophthalmoscopic changes in animals receiving 1.5 mc./cm.^2 were similar but the initial changes were not observed until five or six weeks after implantation.

Consistent ophthalmoscopic changes were not observed in animals receiving 1.0 mc./cm.^2 . Rarely, an ill-defined slightly pale area was noted over the implantation site seven to nine weeks after the procedure. In animals receiving 0.64 mc./cm.^2 or less, ophthalmoscopic changes did not occur.

HISTOLOGIC CHANGES

The rabbits were killed at intervals after implantation with intravenous pentobarbital sodium and the eye having the polyethylene implant was enucleated immediately. Following fixation in neutral formalin solution, nasal and temporal calottes were removed and the eye was embedded in paraffin. Serial sections were stained with periodic acid-Schiff, alcian blue, and toluidine blue in addition to hematoxylin and eosin.

There were no histologic lesions demonstrated in animals receiving between 0.18 and 0.64 mc./cm.^2 of radiation. The eyes were enucleated from eight to 58 weeks after instillation of radioactive iodine in the implanted envelopes.

Of 11 animals treated with 0.90 to 1.0 mc./cm.^2 of radiation, histologic changes occurred in four. Three of these animals

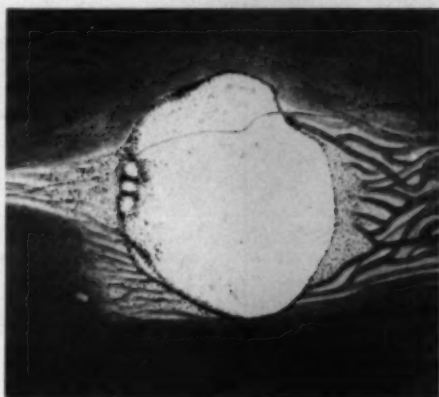


Fig. 4 (Newell, Choi, Book, Harper and Simkus). The fundus lesion in a pigmented rabbit seven weeks after the instillation of 2.0 mc./cm.^2 .

were killed at eight weeks after implantation and one was followed for 58 weeks. The affected animals showed thinning of the choroid adjacent to the envelope and no changes in the pigment epithelium. The layer of rods and cones was degenerated and rarefied and only loose, pale-staining fragments were present. The external limiting membrane and outer nuclear layer in the corresponding area were thinned and there was a decrease in cell population (fig. 5). In the animal killed at 58 weeks, in addition to the changes just described, the pigment epithelium was flattened and there was rarefaction of the outer plexiform and inner nuclear layers.

In all animals receiving an application of $1.50\text{--}2.0 \text{ mc./cm.}^2$, definite ophthalmoscopic and histologic changes occurred. After one week the layer of rods and cones was destroyed and there was thinning of the corresponding outer nuclear layer. The remainder of the eye appeared normal (fig. 6).

After 12 to 26 weeks the choroid was nearly entirely destroyed with few or no blood vessels remaining. The pigment epithelium was thinned and the remaining cells were flat and degenerated and of a spindle rather than cuboidal shape. In some areas there was migration of the pigment epithelium into the region of the degenerated

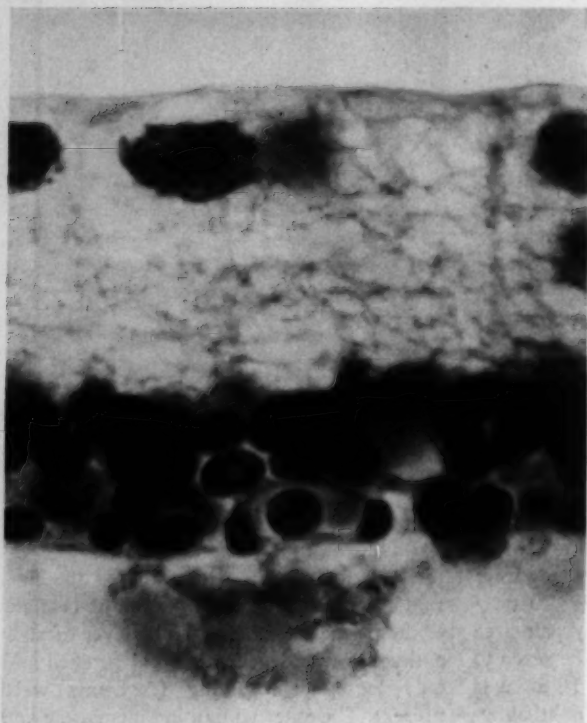


Fig. 5 (Newell, Choi, Book, Harper and Simkus). Destruction of the outer retinal layers with preservation of the internal in an animal killed eight weeks after the implantation of 0.9 mc./cm.² (Hematoxylin-eosin, $\times 1425$.)

retina (fig. 7). After eight weeks, the remaining retina consisted of a rarefied inner nuclear layer and a few ganglion cells (fig. 8).

Hemorrhages were not observed at any

time. There was no phagocytosis or cellular infiltration noted. Lens opacities were not observed and the retina on the side of the eye directly opposite to the site of implantation was not affected.

Fig. 6 (Newell, Choi, Book, Harper and Simkus). Destruction of the layer of rods and cones and rarefaction of the outer nuclear layer in animal killed one week after the implantation of 2.0 mc./cm.² (Hematoxylin-eosin, $\times 190$.)

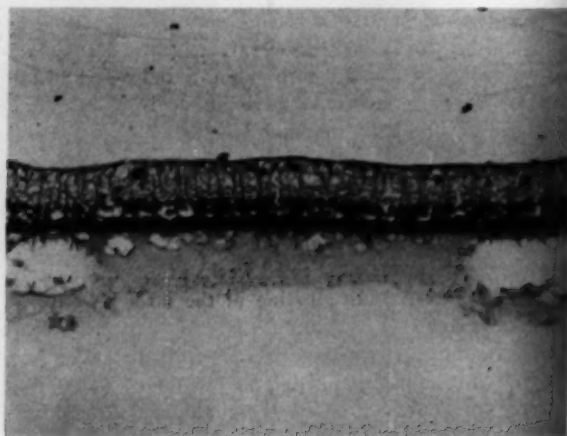
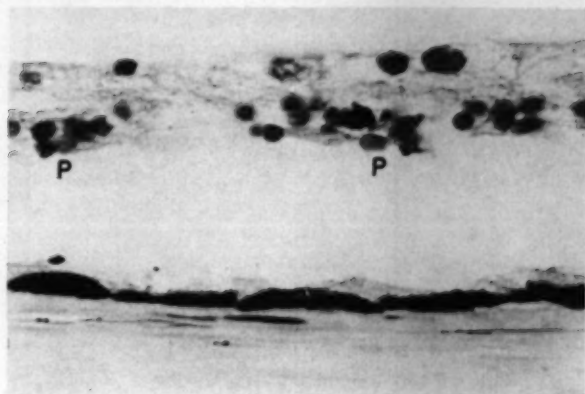


Fig. 7 (Newell, Choi, Book, Harper and Simkus). Destruction of the choroid and migration of pigment epithelial cells (P) into surviving retina in animal receiving 2.0 mc./cm.^2 with eye enucleated after 12 weeks. (Alcian blue, $\times 1085$.)



DISCUSSION

The plastic envelope described, although well tolerated by the ocular tissues, is far from satisfactory. The thin polyethylene is easily perforated by fixation forceps and, in man, the posterior scleral sutures may be difficult to insert. If not adequately sutured the envelope does not conform to the scleral curvature and the retina receives less than the calculated radiation.

Studies indicate that the radioactive iodine is evenly distributed, an essential fac-

tor in dosimetry so that there are no "hot spots" of concentrated radioactivity. It may be well also to shield the surface of the envelope not in contact with the globe to minimize radiation to extraocular orbital structures. A thin foil of either lead or platinum would be effective. Conversely, there were no radiation effects observed in either Tenon's capsule or the overlying rectus muscles with the envelopes used without shielding.

The absence of morphologic evidence of radiation injury to the sclera was somewhat

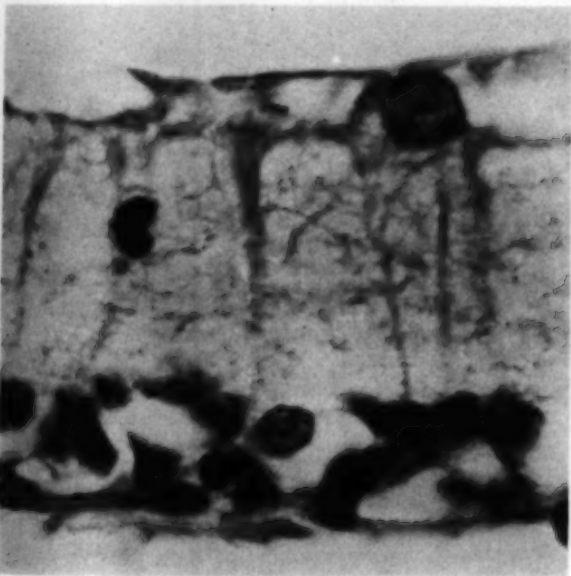


Fig. 8 (Newell, Choi, Book, Harper and Simkus). Thinning of the retina in rabbit with implantation of 2.0 mc./cm.^2 with eye enucleated after 26 weeks. The layer of rods has disappeared entirely and there is a decrease in the number of cells in the inner nuclear and ganglion cell layer. (Hematoxylin-eosin; $\times 1425$.)

surprising, inasmuch as iodine¹³¹ decays by the emission of both beta particles and gamma rays. The beta particles have maximal energies of 0.60 mev (million electron volts) (87.2 percent), 0.335 mev (9.3 percent), 0.250 mev (2.6 percent) and 0.815 mev (0.7 percent) and an average energy of 0.199 mev. The effect of the beta radiation arising in this application is to cause a very high cauterizing dose within 1.0 mm. of the implant. The other radiation effects arise from gamma ray emission. Harper, et al.¹⁰ have implanted envelopes containing iodine¹³¹ adjacent to major blood vessels without causing histologic alteration. It is believed that it is unlikely that delayed scleral radiation injury will be observed with this technique. Radiation cataract was not observed but this may well be due to an inadequate period of observation.

If the technique of focal irradiation is to be maximally useful, the isotope used should be inexpensive and easily available. We believe that it is desirable to permit the implant to remain in position and not to have to remove it after therapy. Table 2 indicates the dosage factors relating to various common isotopes. If the roentgens per hour per curie 1.0 cm. from the source are known, the Paterson and Parker tables may be used in calculation of dosage and comparison of radiation with radium.

In addition to the physical characteristics of radiation, the isotope must be soluble enough to be distributed in the polyethylene envelope and in the event of escape from the envelope must not have undesirable biologic actions. (It should be noted that, when these envelopes are used in man, the thyroid is protected by a prior dose of intravenous potassium iodide.) With these considerations iodine seems to be the most satisfactory isotope for this application.

The cytologic changes observed in the rabbits reported here are generally comparable to other experimental studies of the effects of ionizing radiation upon the posterior ocular segment. Cibis and his co-workers irradi-

TABLE 2
CALCULATED GAMMA RADIATION LEVELS FOR ONE MC
OF SOME RADIOISOTOPES

Isotope	r/hr./ mc. (A) at 1.0 cm.	Mean Life (B)	Total Dose (D)
Radium (0.5 mm. pt. filtra- tion)	8.4	2284 yr.	1.68×10^8 r
Radon	8.4	133 hr.	1117 r
Cobalt ⁶⁰	13.5 (E)	7.6 yr.	8.66×10^8
Gold ¹⁹⁸	2.48	93 hr.	223 r
Iodine ¹³¹	2.31	280 hr.	630 r
Iridium ¹⁹²	5.1 (C)	101 da.	1.24×10^8 r
Tantalum ¹⁸²	6.13 (C)	159 da.	2.34×10^8 r

A. From Overman, R. T., and Clark, H. M.: Radioisotope Techniques, New York, McGraw-Hill, 1960.

B. The time required for the disintegration rate to decrease by the factor e^{-1} :

$$\frac{\text{half-life}}{0.693} = \text{half-life} \times 1.443$$

C. Lederman, M., and Sinclair, W. K.: Radioactive isotopes for beta and gamma ray applicators. In Therapeutic Use of Artificial Isotopes (Paul F. Hahn ed.), New York, John Wiley & Sons, 1956.

D. Assuming complete decay, no absorption, inverse square attenuation, a plane applicator measured at a distance of 1.0 cm.

E. By calculation from Stallard's data the value for cobalt⁶⁰ with the shielding used by him is about 9.0 r/hr./mc. at 1.0 cm.

ated the entire eye using a variety of sources but mostly X-radiation. A dose rate of 630 r/min. in air and 275 r/min. in vitreous was used. This corresponds to a dose rate of 0.077 r/min. at a distance of 1.0 cm. from the applicator when iodine¹³¹ is used. It must be remembered, however, that inverse square attenuation resulted in a much higher dose near the retina. However, even if the retina was 1.25 mm. from the source the maximum radiation was 0.616 r/min.

In the dosage used here, acute vascular congestion and systemic radiation effects, as observed by Cibis, et al., did not occur. The outer retinal layers, particularly the layer of rods and their nuclei, appeared much more sensitive to ionizing radiation than either the remainder of the retina or the choroid. The cytologic changes were a direct result of ionization and did not occur because of interference with the retinal blood supply.

Previous studies of the effects of locally

applied radiation to the posterior ocular segment have arisen mostly from instances of unsuccessful therapy of human malignancy. In these cases there is usually no correlation of factors of dosage and histologic change. However, the report of Tamler, Winter, and Toch¹¹ is unusually detailed and should be repeated in other eyes in which radiation dosage is known.

The dosimetry of radiation of tissues adjacent to implanted radioactive substances is most inaccurate. The isodose curves shown in Figure 1 indicate that, in the region closest to the source, a variation of dosage of a mm. can result in a variation of dosage of thousands of roentgens. However, if one considers the applicator having a half-thickness of 0.5 mm. and the thickness of the choroid and sclera to be 1.5 mm., the minimum dose causing rod damage in this series was 3,300 r and a dosage of 2,400 r did not cause histologic changes. This is assuming, however, that the radioactive source was immediately adjacent to the sclera, an assumption not confirmed by the absence of beta particle damage to the sclera. If it is assumed that the radiation source was 3.0 mm. from the retina rather than 2.0 mm., the dosage factors conform closely to those of Cibis, et al.: 2,040 r caused radiation injury and 1,510 r did not.

Focal ionizing radiation of the posterior globe has been used in the treatment of retinoblastoma, metastatic carcinoma, and malignant melanoma of the choroid. In assessing the effects in retinoblastoma the outstanding results of Reese and his co-workers¹² using X-radiation and intracarotid antitumor agents, particularly triethylene melamine, must be considered. It seems likely, however, that, if less than one third of the retina is involved, either method of radiation will be successful. Focal ionizing radiation has as its advantages a single application of an easily controlled, high dose of radiation precisely localized to the area to be treated, without involvement of overlying structures. It could thus be used in instances in which both

eyes are present, as in the occurrence of the tumor in the offspring of retinoblastoma survivors. The chief disadvantage of focal ionizing radiation is failure to sterilize minute nests of tumor too small to be seen. Additionally, in tumors located in the anterior globe, a cataractogenic dose of radiation may be administered.

The chief advantage of X-radiation is in the accumulated experience with this mode of therapy. However, to achieve the excellent results reported by Reese considerable attention must be directed to the appropriate mechanical devices designed to direct the X-radiation. If such appliances are not available, focal ionizing radiation would appear to offer considerable advantage.

The best method of treating metastatic carcinoma of the choroid is open to question. Generally such tumors are sensitive to radiation and cataract is not a problem in view of the limited life expectancy, so that conventional X-radiation can be used in adequate dosage without extraordinary precaution. However, focal ionizing radiation may be just as effective and applied with less difficulty.

Stallard,¹³ in 1959, reported the use of radioactive applications in the treatment of malignant melanoma of the choroid. Forty-five patients were treated, with success in 25. He points out that it is too early to assess the results. Of the patients treated, 21 had either one eye or a severe disorder in the fellow eye, 11 refused enucleation, and in the remainder the lesion was less than 5.0 mm. in size.

The reports in the literature suggest strongly that in retinoblastoma, if conventional radiation therapy has been used without success, it is extremely unlikely that focal ionizing radiation will preserve the eye. Many of the instances of unsuccessful local application of ionizing radiation involve eyes in which initial X-radiation did not arrest the process.

From the studies reported here it is believed that focal ionizing radiation with io-

dine¹³¹ will give results comparable to those obtained with radium, cobalt⁶⁰ or radon applicators. The chief advantage in the use of iodine¹³¹ is in permanent placement of the implant so that it does not have to be removed. It is believed that a concentration of 2.0 mc./cm.² of iodine¹³¹ should be used with appropriate precaution so that the implant is in close contact with the sclera overlying the area to be treated.

SUMMARY

1. Rabbit eyes were treated with iodine¹³¹ instilled in a polyethylene envelope containing blotting paper. The envelope was sutured to the sclera prior to instillation of the isotope.

2. No ophthalmoscopic or histologic lesions were observed with concentration of 0.18 to 0.67 mc./cm.². A concentration of

0.9-1.0 mc./cm.² resulted, in some animals, in a retinal lesion limited largely to the rod layer, with minor injury to the corresponding external limiting membrane and outer nuclear layer. A concentration of 1.5-2.0 mc./cm.² destroyed the choroid and retina, with a few ganglion cells and inner nuclear layer cells persisting. Damage developed more slowly in animals receiving the lower dosage but the end-results were similar. Cataract did not develop in the limited period of observation, which varied to a maximum of 58 weeks.

3. It is believed that focal ionizing radiation of intraocular tumors is feasible, using the polyethylene envelope and absorbent layer in a minimal dosage of 2.0 mc./cm.² of iodine¹³¹.

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POSTOPERATIVE INTRAOCULAR INFECTIONS*

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INCIDENCE OF INTRAOCULAR INFECTION

Despite the aseptic techniques available for ophthalmic surgery, intraocular infections continue to occur and, although numerous types of antibiotics and chemotherapeutic agents may be employed, the infections frequently fail to respond to treatment.

The incidence of intraocular infections differs in various institutions but is usually less than one percent: Dunnington and Locatcher-Khorazo¹ reported 11 cases of endophthalmitis in 2,508 cataract operations (0.44 percent) in which an antibacterial agent was not used preoperatively; Hughes and Owens² observed 21 patients with endophthalmitis in a series of 2,086 operations (1.01 percent) without preoperative prophylaxis; Berens and Bogart, as cited by Callahan,³ reviewed nine series of postcataract endophthalmitis over an 18-year period (1921-1938) and found the average rate of infection in 6,137 operations to be 0.75 percent, encompassing a range between 0.10 percent and 1.5 percent.

Although most infections appear immediately following surgery, intraocular infections may not be manifest until weeks or years after the operation. They have been

found in filtering blebs as long as 20 years after a fistulizing operation for chronic glaucoma, and this is known to occur in two to three percent of the cases.⁴ Trephine procedures are more prone to postoperative infection than iridencleisis but complications have been reported subsequent to all types of filtering procedures. Fungus infections after cataract operations are often not evidenced for weeks or months.

ETIOLOGIC MICRO-ORGANISMS

Most intraocular infections are caused by one or more of the following bacteria: staphylococci, streptococci, pneumococci, *E. coli.*, *Pseudomonas aeruginosae*, and the *Proteus* species; penetrating wounds may be contaminated with *Clostridium welchii* or *Bacillus subtilis*.

In recent years, staphylococci—particularly the aureus species and antibiotic-resistant strains⁵—have been encountered in preoperative eye cultures with increased frequency. However, as opposed to other parts of the body, there has been no demonstration of a concomitant increase in the number of ocular infections caused by these antibiotic-resistant bacteria.

No one has shown that viral infections in the postoperative period have become more prevalent but attention has been called to the possibilities of intraocular infection with varieties of fungi. It has been suggested

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that fungal infections have increased by virtue of the use of local antibiotics and steroids for other purposes. The fungi responsible for intraocular infection include species of *Actinomyces*, *Aspergillus*, *Blastomycetes*, *Candida*, *Cephalosporium*, *Cladosporium*, *Curvularis*, *Gibberella*, *Penicillium*, and *Volutella*.⁶ Intraocular mycotic infections, presumably a hematogenous spread from an infection elsewhere, have occurred spontaneously from an extension of a fungus infection of the cornea, and from a surgical or traumatic penetration of the globe.

In 1902, Römer⁷ found abscesses which harbored *Aspergillus fumigatus* in the anterior vitreous of a child's globe damaged with a knife. Other authors have also elaborated intraocular mycotic infections after injuries to the eye.⁸⁻¹¹ Most of the recorded postoperative intraocular fungal infections have followed cataract procedures.¹¹⁻¹⁵ Budek's¹⁶ case was a consequence of retinal detachment surgery.

The report by Verhoff,¹³ in 1924, is particularly interesting in that an infection (actinomycotic granules)⁷ developed in the operated eye and subsequently appeared in the contralateral eye. He concluded that the fungal infection developed during surgery and spread hematogenously from one eye to the other. In the histopathologic study of 13 globes by Fine and Zimmerman,¹¹ the authors were unable to identify the fungi definitely. They conjectured the majority to represent species of *Aspergillus*, *Cephalosporium*, *Fusarium*, or *Volutella*. In none of their cases were the budding yeast forms suggestive of the *Candida* species observed, nor were any actinomycotic granules detected.

SOURCE OF INFECTION

Diverse sources of exogenous intraocular infection are known to exist. Bacteria or fungi can be introduced into the globe by contaminated surgical instruments or irrigating fluid, or one of the medications instilled during or after surgery may not be

sterile. Foreign material such as cotton fibers, talc, or starch granules may harbor the spores of fungi.

Posner¹⁷ believes the introduction of cornstarch glove powder during the past decade has been a factor in the increase of surgical infections, the particles serving as reservoirs for fungi and air-borne bacteria and as an organic base to support their growth.

Another source are micro-organisms which may be either on the skin in the operative field or in the cul-de-sac and carried into the eye. Relative to the latter possibility are the bacteriologic studies of the normal fungal flora of healthy eyes.

Fazakas,¹⁸ a Hungarian, obtained positive cultures for fungi in 24 percent of 160 normal eyes. Mitsui and Hanabusa,¹⁹ Japanese workers, cultured fungi in 12 of 65 healthy eyes (18.5 percent). Recently, Hammeke and Ellis⁶ from the United States studied the mycotic flora of the normal conjunctival sacs of 529 eyes of healthy adults, children and newborns. Cultures were positive in 10 percent of the adult eyes, five percent of the children's eyes, and 0.1 percent of the newborns' eyes. Four of the species of fungi were listed among the 10 which had been isolated in reported cases of mycotic endophthalmitis.

It has often been suggested that the widespread use of corticosteroids and antibiotics in the pre- and postoperative care of the patient might be responsible for the apparent increase in intraocular fungal infections following surgery. Mitsui and Hanabusa,¹⁹ studying the propagation of fungi in the conjunctival sac after prolonged local corticosteroid therapy, found 42 of the 62 patients (67 percent) to have a positive culture for fungi, whereas, as mentioned previously, a control group in which no cortisone was used yielded fungi in 18.5 percent of the cases. The fact that the severity of *Candida* keratitis has increased by the application of local steroids appears true with regard to all of the available corticosteroids.

Ley²⁰ has suggested that an antibiotic such

as oxytetracycline may potentiate *Candida albicans* infection in the immature rabbit cornea. Tanaka,²¹ however, held that the use of topical antibiotics in the eye did not favor fungal infection. She noted *Candida albicans* in the conjunctiva after local antibiotic treatment (three in 40 cases) to be no more prevalent than in a group of control cases (two in 35). In an in vitro test, the growth of *C. albicans* was observed to be inhibited by oxytetracycline and chlortetracycline at a concentration of 0.25 percent but the growth of the fungus was stimulated at a concentration of less than 0.01 percent. (Most tetracycline preparations for topical use in ophthalmology have a concentration of 0.5 percent or higher.)

Several years ago, Choi,²² working at the Wills Eye Hospital, was able to demonstrate in rabbits that a self-limiting type of intraocular infection, produced by the inoculation of small numbers of *Candida albicans* fungi into the choroid, could be changed into a serious type of infection by the use of steroids given in the second or third week after the initial inoculation. In recent attempts in the same laboratory to confirm the observations of Choi, difficulty has been encountered. The fungi have apparently been highly virulent, for severe infections could be produced readily by direct inoculation of the fungi into the choroid or into the cornea. While fungi have not required potentiation by corticosteroids or antibiotics for the production of serious infection, steroids continue to enhance the severity of the existing infection.

Other ocular factors that may contribute to an increased incidence of postoperative infections are: excessive surgical trauma, extensive operations (for example, retinal detachment procedures), and the implantation of foreign bodies such as polyethylene tubing and nonabsorbable sutures in the eye. In a consideration of postoperative eye infections, Burns²³ concluded that multiple operations and "weak ocular tissue" (high myopia, congenital nystagmus, retinal degeneration, and

detachment after uneventful cataract extractions) were prime causative factors.

There are nonocular conditions which are thought to increase the susceptibility of patients to postoperative infection. These include severe metabolic disturbances such as diabetes, serious neoplastic disease (especially if the patient has received potent anticancer drugs or irradiation), advanced age, suboptimal nutrition, and poor general health.

PREVENTION OF INTRAOCULAR INFECTION

The extreme difficulty of establishing an etiologic diagnosis in the presence of an intraocular infection is well known. This is particularly true with fungus endophthalmitis, where the procurement of a suitable specimen for culture is most unlikely. If fungi are inoculated into the eye and attempts made to recover them by extraction of the aqueous or vitreous humor, these attempts are usually unsuccessful.²⁴ Sery experienced the same problem with mycotic keratitis.²⁴ Even with bacterial infections in which a known inoculum has been made into the eyes and an obvious infection produced, recovery of the bacteria, particularly from the aqueous humor, is not always successful.²⁵ Fine and Zimmerman²¹ have suggested a greater possibility of obtaining a positive culture by needle extraction of fluid if the responsible fungi were organisms such as *Cryptococcus neoformans* or *Histoplasma capsulatum* which remain in tissues as yeast rather than mycelial forms. There is also substantial evidence that once infection has been established it is difficult to control, for we do not yet have adequate antifungal medication for all the potential invaders.

Prevention, therefore, is our first aim. Strict attention must be given to the preoperative preparation of the patient. The use of antibiotics and corticosteroids should be avoided when possible. There is the evidence that the use of antibiotics for extended periods encourages the appearance of microorganisms ordinarily not present, such

as *Pseudomonas aeruginosa* or fungi, or the development of bacteria which might otherwise not be sufficiently virulent unless their competitors were destroyed or inhibited. We have cited evidence that corticosteroids facilitate fungal growth and infection. Insufficient data exist at the present time to determine the effect of short-term usage of antibiotics (two or three days) on the development of fungal infections or resistant micro-organisms such as staphylococci, *B. proteus* and *Pseudomonas aeruginosa*.

The area about the eyes and the conjunctival sac should be thoroughly cleansed and irrigated with antibacterial and antifungal agents immediately before the operation. This should be performed with the aim of mechanically removing any fungal spores, cotton fibrils, talc, or starch granules which inadvertently may have come in contact with these areas. All solutions and instruments should be sterilized and carefully handled in order to insure the prevention of any source of infection.

Prophylactic antibiotic therapy has been most successful in guarding the patient from invasive infections in selected instances: reducing recurrent attacks of rheumatic fever, protecting the patient with valvular heart disease against the development of subacute bacterial endocarditis, and in promoting effective surgery in the presence of a contaminated field. For patients who must receive high doses of corticosteroids, the benefits from prophylactic antibiotic therapy are still subject to conjecture. Antibiotic prophylaxis has generally been extended from a well-defined procedure for presented situations to a routine in all surgical risks. Accordingly, there is reason to evaluate the significance and efficiency, as well as the safety, of this practice. The cliché that this type of prophylaxis and subsequent treatment with antibiotics "might help but can't do any harm" is no longer tenable. Control studies by general surgeons indicate the impracticality of the routine administration of antibiotics before and after surgery to

control postoperative infections.²⁶⁻²⁹ The prophylaxis was either ineffective in preventing postoperative infections or associated with bacterial complications more often than the untreated group.

Knowledge concerning antibiotic surgical prophylaxis relative to other organs cannot necessarily be constructively applied to the eye. However, there is much sentiment in opposition to routine antibiotic prophylaxis. No definitive studies have been conducted to validate its supposed effectiveness, and, furthermore, the recent decrease in intraocular infections could as easily be attributed to more adequate selection and preparation of patients prior to surgery than to the treatment itself. Extensive criticism has been evoked on the subject of this therapeutic approach: the tendency on the part of the surgeon to become lax in his aseptic technique, side-effects of the drugs to which the patient is unnecessarily disposed, the stimulation of resistance to bacterial strains—perhaps also to fungi and even possibly to viruses—and the waste promoted by widespread usage. Evidence that fungal infections might be augmented by short-term antibiotic prophylaxis is not well established, although Ley³⁰ did demonstrate successfully that oxytetracycline would render the fungi more infectious on the cornea.

There are definite limitations in the use of antibiotic prophylaxis, among which are the facts that no single antibiotic is universally effective, blood aqueous barriers may prevent contact of the antibiotic with the infective bacteria, and therapy must be selective in spite of the absence of specific information necessary to identify the micro-organism producing the infection. However, the most common infecting agents for the past few years are known, and the antibiotic prophylaxis may satisfactorily be directed against them.

Aside from the contraindications suggested, the institution of prophylactic therapy offers certain advantages: permitted to become established, infection poses a greater

difficulty to control, in addition to which the use of this therapy in adequate dosage, even if the offending micro-organism is not responsive and infection does occur, serves to furnish valuable information regarding a plausible etiologic agent and thereby reduces the selective range of antibiotics for active therapy.

A decrease in the occurrence of postoperative eye infections with the use of antibiotics prior to or at the time of surgery has been reported. Locatcher-Khorazo and Gutierrez⁵ noted 11 cases of endophthalmitis in a control study including 2,508 cataract operations (0.44 percent), whereas after a routine preoperative application of an antibiotic ointment locally, only six cases in 7,662 operations were observed (.08 percent). Hughes and Owens² experienced 21 patients with endophthalmitis in a series of 2,086 operations for the removal of cataract (1.0 percent) in the absence of preoperative antibacterial therapy, compared with two such complications in 1,200 operations (0.17 percent) in which topical antibiotics were used before surgery. Pearlman³⁰ reported a correspondence between prophylactic subconjunctival penicillin and streptomycin after cataract extraction and the prevention of concomitant postoperative endophthalmitis. Prior to their use, nine of 1,773 postcataract eyes (0.51 percent) developed intraocular infection, although precautions, preoperatively and aseptically as well as pre- and postoperative local antibiotic medication, were exercised. No infections appeared in 3,226 postcataract eyes given the subconjunctival injection. Whereas these data tend to support the value of prophylactic antibacterial therapy, the effectiveness of this program will be proven only as a consequence of a controlled study both instituted and performed by a single ophthalmic surgeon or surgical team.

The role of preoperative eye cultures relative to postoperative infections is a subject of dispute. Many ophthalmologists choose to operate only after the culture, secured prior to surgery, is found to be

negative. Others consider routine eye cultures not essential and establish the single condition that no gross signs of infection be present in or about the eyes.

Dunnington and Locatcher-Khorazo¹ advocate the use of eye cultures preoperatively. Their study of infections following cataract extraction indicated that the presence of *Staphylococcus aureus* before surgery corresponded to the occurrence of postoperative infection, while its absence was found to be coincident with the existence of no infections.

Burns,²³ in a more recent study of postoperative infections at the same institution, reflected that routine bacteriologic study before operation "did not seem to be of great help." The bacteria which had been isolated from the clinically noninfected eye were often of low pathogenicity as determined by laboratory tests, and, accordingly, not responsible for postoperative infection. In Burns' series, 11 wound infections were observed in a total of 8,038 operations (0.14 percent). All presented staphylococcus in a pure or mixed culture, while four had actually been treated with a prophylactic antibiotic ointment. Included in 2,695 cataract extractions in this group were five postoperative infections (0.19 percent).

Callahan⁸ indicated that the information obtained from preoperative cultures has been a factor in reducing the incidence of postoperative panophthalmitis in cataract extractions. He experienced five cases of panophthalmitis in the course of 1,653 operations and appreciated the importance of both detecting and eliminating gram-negative bacilli which appeared in cultures of the conjunctiva and eyelids before surgery.

It is evident both from personal experience and data in the literature that a preoperative eye culture does not provide an adequate indication of whether or not postoperative infection will occur. Infections have been observed after sterile preoperative cultures and have been absent when highly pathogenic bacteria (for example, "epidemic" 80-81

strain of *Staphylococcus aureus*) have appeared in the pre- and postoperative cultures.²³

If antibiotic or chemotherapeutic agents are to be used prophylactically, they must be used as an adjunct to, and not a substitute for, an aseptic surgical technique or the reduction of regional bacterial flora by mechanical cleansing. The employment of preoperative local antibacterial therapy renders advisable the use of agents not ordinarily given systemically. Neomycin, polymyxin, and bacitracin, for instance, are known to produce toxic side-effects when given systemically and are therefore rarely used for infections not conveniently treated locally. A patient treated with one of these agents locally who develops a local sensitivity reaction will not be adversely affected if serious body infections are subsequently encountered. For systemic use, antibacterial drugs should be given in that dosage and route of administration which will provide adequate antimicrobial concentrations in the potentially infected tissues. As a function of the blood-ocular barrier, drugs must be given in higher doses than usually prescribed for other infected sites.

The choice of drugs for prophylaxis is most ideally made after bacteriologic study; otherwise, the selection should be guided by knowledge of the etiologic micro-organisms found in other cases of postoperative infection and by prior experience in one's own institution.

Those physicians who attempt to sterilize the eye area completely with preoperative antibacterial therapy are advised to review the work of Locatcher-Khorazo and Gutierrez⁵ which appraises the time required to eliminate and suppress bacteria with local eye treatment. Preoperative antibiotic medication (at least five local applications) eliminated *Staphylococcus aureus* in two days in more than half the patients studied but required as long as five days in a small number of cases. Elimination of *E. coli* and *B. proteus* required treatment for three to five days.

Suppression of growth by the treatment was only temporary, the bacteria in the non-operated eye reappearing in most instances with 24 hours after the operation, or, in the remaining cases, within two to seven days. These data afford an indication of that duration of time, before and after operation, required to maintain the eye in a sterile condition with local antibiotic therapy.

The continuation of local antibiotic or chemotherapeutic agents during the postoperative period is apparently necessary for the reduction of the bacterial flora. However, the influence of such therapy on the propagation of fungi in the cul-de-sac has not been definitely ascertained. Theoretically, tolerable concentrations of quaternary ammonium compounds, or mercurials, might reduce fungal as well as bacterial flora after local instillation.

Locatcher-Khorazo and Gutierrez²¹ utilized bacteriophage typing in a study of the *Staphylococcus aureus*, regarded as the principal pathogen in postoperative eye infections, to differentiate individual strains of the micro-organism. In contrast to the epidemic staphylococcal infections in other hospital areas, the *Staphylococcus aureus* ocular infections were not found to have been caused by one or several phage strains. Whereas a large variety was isolated from normal eyes, only one strain was consistently isolated from the areas adjacent to the eyes, nose, and skin of an individual patient. This single strain was observed to persist as long as 15 months and, although antibiotic therapy eliminated the staphylococci, the same phage type reappeared soon after the discontinuation of treatment. In ocular infections, including those of unilateral postoperative origin, a specific phage type was seen not only in the infected eye but in the noninfected eye, the nose and throat, and contiguous skin areas as well. The phage types of staphylococcus isolated in the cases of postoperative endophthalmitis were identical to those detected in the preoperative cultures when these studies had been performed.

Although the routine exercise of prophylactic antibacterial therapy before and after an operation is subject to conjecture, some justification for the practice is found in certain instances: (a) one-eyed patients, (b) extensive operative procedures, (c) patients with "weak ocular tissue" as described by Burns,²³ (d) multiple operations, particularly if performed within short intervals, (e) operations on the contralateral eye during a single confinement, (f) subsequent to extracapsular extractions (the lens material can favor bacterial growth), (g) patients with serious metabolic or neoplastic diseases, (h) elderly or feeble individuals.

ACTIVE THERAPY

The cardinal prerequisite of successful antimicrobial therapy is, of course, the selection of the proper drug. Theoretically, the infecting micro-organism should be identified and its sensitivity to the various drugs be determined. However, the exigency in terms of treatment for the intraocular infection may preclude the initiation of an etiologic diagnosis; moreover, negative cultures are frequently encountered in the presence of obvious clinical signs of infection. In order to obviate the loss of vision, and aware of its imminence, treatment must be prompt and vigorous. Intimate familiarity with the types of micro-organisms, previously enumerated, which have been successfully recovered in cases of human intraocular infections is indispensable. The therapeutic program may be further influenced by the results of the eye smear and culture and sensitivity tests, determining a continued or altered course.

Antimicrobial drugs can be classified as bacteriocidal, those which kill bacterial organisms, or bacteriostatic, those which inhibit growth and multiplication (multiplication resuming after removal of the drug). The difference is primarily quantitative; a single drug assumes either bacteriostatic or bacteriocidal proportions as a function of the level of concentration and the period of exposure.

Drugs in common use which behave primarily as bacteriocidal agents include penicillin, bacitracin, ristocetin, vancomycin, streptomycin, polymyxin B, neomycin, kanamycin, colistin and the nitrofurantoin-furaldone (Altafur). Those characteristically serving as bacteriostatic agents are erythromycin, oleandomycin, spiramycin, novobiocin, carbomycin, the tetracyclines, chloramphenicol, soframycin, amphotericin-B, and the sulfonamides.

The antibacterial spectrum of antibiotics can most conveniently be remembered by dividing pathogens into rods and cocci, most of which are, respectively, gram-negative and gram-positive. Bacteriocidal drugs which predominantly destroy cocci are penicillin, bacitracin, ristocetin, and vancomycin and those which primarily kill rods are streptomycin, colistin, and polymyxin; neomycin, kanamycin and furaldone are effective for a wide variety of both rods and cocci. Bacteriostatic antibiotics acting basically on the cocci are erythromycin, spiramycin, oleandomycin, novobiocin and carbomycin. The broad-spectrum antibiotics, the tetracyclines and chloramphenicol, and the sulfonamides are active against rods in addition to cocci.

Since the initiation of therapy often precedes the results from smears, cultures, and sensitivity tests, recourse to an antimicrobial drug or combination of drugs possessing a wide spectrum of activity will permit the destruction of the etiologic organisms, whether gram-positive or negative. A therapeutic drug level is usually gained most promptly by a combination of systemic and subconjunctival therapy. The existence of the blood-ocular barrier normally requires an elevated systemic dose, yet its effect is diminished in the presence of inflammation.

The rate of penetration with which the various drugs gain entrance to the ocular fluids varies and this factor emphasizes the importance of an intimate familiarity with both the dosage and penetration characteristics of each drug (table 1). Chloramphenicol is an appropriate drug with which to initiate

TABLE 1
DOSAGE FOR SYSTEMIC THERAPY IN INTRAOCULAR INFECTION
(Listed in order of preference)

Agent	Dosage
A. Effective against gram-positive and gram-negative organisms	
1. Chloramphenicol	3 gm. priming dose—oral or I.M. 1 gm. every 8 hr.
2. Kanamycin (Kantrex)	3 gm. priming dose—I.M. 1 gm. every 8 hr.
3. Penicillin with streptomycin	1 million units I.M. every 6 hr. (Benemid to enhance level) 1 gm. I.M. every 8 hr.
4. Tetracyclines: demethylchlor—(Declomycin)	2 gm. priming dose—oral 1 gm. every 8 hr.
5. Sulfonamides Sulfadiazine	4 gm. priming dose—oral 1 gm. every 4 hr.
Sulfamethoxypridazine (Kynex, Midicel)	1 gm. priming dose—oral 0.5 gm. every 12 hr.
B. Primarily effective against gram-positive infections (especially penicillin-resistant Staph.)	
1. Erythromycin —propionate (Ilosone)	2 gm. priming dose—oral 1 gm. every 8 hr.
—succinate (Erythrocin)	100 mg. every 4 hr.—I.M.
2. Oleandomycin: triacetyl—(Cyclamen, TAO)	3 gm. priming dose—oral 1 gm. every 8 hr.
3. Novobiocin (Albamycin, Canthomycin)	2 gm. priming dose—oral 1 gm. every 8 hr.
4. Vancomycin (Vancocin)	2 gm. priming dose—I.V. 1 gm. every 8 hr. $\times 7$ doses 1 gm. every 12 hr.
5. Spiramycin	3 gm. priming dose—oral 1 gm. every 8 hr.

therapy because it diffuses well into the intraocular tissues and fluids, has a wide spectrum of antibacterial activity, and is effective against many of the staphylococci which have become resistant to penicillin.³²⁻³⁷

Our order of preference for the inauguration of systemic therapy with unidentified etiologic micro-organisms has been chloramphenicol, kanamycin, penicillin with streptomycin, and a tetracycline, all of which have a wide antibacterial spectrum. An antibiotic such as erythromycin, triacetyloleandomycin, novobiocin, spiramycin, or vancomycin—in combination with a drug which acts against gram-negative organisms, such as streptomycin or chloramphenicol—theoretically also

would be satisfactory. Neveu and Elliot³⁸ have reported the use of erythromycin and sulfisoxazole (Gantrisin) in the prophylaxis and treatment of intraocular infections. We have not used sulfonamides initially in the active treatment of postoperative endophthalmitis because their bacteriostatic effect is significantly reduced by the presence of purulent material.

As part of the initial treatment of such postoperative infections, we recommend that subconjunctival medication be given in conjunction with systemic therapy. The drugs should be effective against gram-positive and gram-negative bacteria and exclude those employed for systemic therapy, allowing greater

TABLE 2
DOSAGE FOR SUBCONJUNCTIVAL THERAPY
IN INTRAOCULAR INFECTION

Agent	Dose
A. Listed in order of preference	
1. Neomycin	100-500 mg.
2. Bacitracin	10,000 units
plus	
Polymyxin B	5.0-10 mg.
3. Erythromycin	2.5 mg.
or	
Novobiocin	15 mg.
plus	
Polymyxin B	5.0-10 mg.
4. Penicillin	500,000 units
plus	
Streptomycin	50 mg.
5. Soframycin	250-500 mg.
B. Alphabetical listing of additional agents	
Amphotericin-B	15 µg.
Carbomycin	2.5 mg.
Chloramphenicol	1.25 mg.
Kanamycin	10-20 mg.
Oleandomycin	1.25 mg.
Spiramycin	10-20 mg.
Tetracyclines	2.5 mg.

opportunity for the pathogen to be susceptible to at least one of them. A list of drugs which can be given subconjunctivally, including the dosage, is provided in Table 2. Our selection has been neomycin or bacitracin with polymyxin B, the latter being the most readily available potent antibiotic for *Pseudomonas aeruginosa* (*B. pyocyaneus*) infections, although colistin may prove to be equally applicable.³⁹ Large doses (500 mg.) of neomycin subconjunctivally are also effective against this organism,⁴⁰ as apparently is soframycin which has been successful against many gram-positive and gram-negative organisms, including many strains of *Pseudomonas aeruginosa* and *B. proteus*.⁴¹⁻⁴² Our next choice would be erythromycin or novobiocin combined with polymyxin B, then penicillin with streptomycin. Occasionally, dictated only by the gravity of the condition, intraocular injection of antibiotics may be used (table 3).

It has been our policy to select new antibiotics and commence ACTH or corticosteroid therapy if no improvement is observed after the first 24 hours of treatment. The choice of this medication should be based

on bacteriologic aids and, if these studies are negative, other antibacterial drugs are chosen which again are theoretically effective against both gram-positive (especially antibiotic-resistant staphylococci) and gram-negative (*Pseudomonas*, *B. proteus*, *E. coli*) bacteria. ACTH or corticosteroid therapy is begun at this time to reduce the inflammatory reaction within the eye. Profound visual loss can be caused by the inflammatory damage during the time the antibiotic therapy is gaining control of the infectious agent, a consideration which may render an earlier administration of ACTH or corticosteroid therapy advantageous.

The simultaneous treatment with cortisone and antibiotics has been more successful than antibiotic therapy alone as shown by previous studies on experimental intraocular infection.²⁸ Corticosteroid therapy has apparently not interfered with the control of an infection when the infecting organisms are sensitive to the antibiotic and the dose of the antibiotic adequate.

Corticosteroids or ACTH are used by us after antimicrobial failure in the first 24 hours of treatment; prior to this time the anti-inflammatory nature of these agents might mask the influence of the antibiotic on the infection.

ACTH is regarded by some workers as a more effective, or physiologic, anti-inflammatory agent than the corticosteroids because the hormone may mobilize an entire spectrum of adrenal steroids rather than a single component, while other authorities consider this

TABLE 3
SOLUTIONS FOR INTRACAMERAL INJECTION OR IRRIGATION

Antibiotic	Concentration
	(per ml.)
Amphotericin-B	500 µg.
Bacitracin	500-1000 units
Carbomycin	1-2 mg.
Chloramphenicol	1-2 mg.
Erythromycin	1-2 mg.
Neomycin	2.5 mg.
Penicillin	1000-4000 units
Polymyxin B	0.1 mg.
Streptomycin	0.5-5 mg.
Tetracyclines	2.5-5 mg.

a theoretical advantage with no clinical significance. The limited secretory capacity of the adrenal cortex is regarded to offer a disadvantage to ACTH therapy by the establishment of an arbitrary dosage beyond which additional ACTH has no effect, a restriction not characteristic of corticosteroid therapy. Perhaps the maximum and most expedient action can be achieved by the simultaneous administration of ACTH and a parenteral corticosteroid.

ACTH is contraindicated in patients having recently received corticosteroids in order that adrenal hypofunction, potentially induced by the treatment, is not encountered.

During the period in which this routine has been employed, we have observed that both globes and vision were salvaged which heretofore would not have been possible. Pico⁴³ has also reported favorable visual outcome in cases of postcataract endophthalmitis with this general plan of treatment.

INDIVIDUAL ANTIMICROBIAL DRUGS

PENICILLIN

Despite the introduction of many new antibiotics, penicillin remains the most effective antibiotic against gonococci, Treponema organisms, and the gram-positive infections including all sensitive strains of staphylococci (many strains of which are now penicillin-resistant), pneumococci, hemolytic and non-hemolytic streptococci, anthrax, actinomycosis, tetanus, clostridial infections, and fusospirochetal diseases. In the penicillin-sensitive patient with these infections, other antibiotics such as erythromycin propionate must be used.

Penicillin should be avoided if there is a history of previous penicillin reaction or allergic diseases, or in the presence of active tinea infections of the skin. An additional measure of precaution is afforded by a scratch test, which is both more reliable and safe than intracutaneous or ocular tests. The treatment for immediate penicillin reactions is parenteral epinephrine. Antihistamines, corticosteroids, and penicillinase (Neutrapen) are most advisely reserved for the

treatment of delayed penicillin reactions.

Penicillin G is the most extensively employed of all the antibiotics, affording maximum potency and minimum toxicity. The sodium and potassium salts of this drug, prepared for injection in aqueous solution, are absorbed rapidly and favored in acute infections. Maximum plasma concentrations develop in 15 to 30 minutes after injection and disappear within three to six hours, depending on the dosage. Forms of oral penicillin, including the synthetic preparation Syncillin, do not insure the establishment of an adequate blood level and are not recommended for serious intraocular infections.

The normal blood-ocular barrier presents an impediment to the accessibility of aqueous penicillin^{44,45} to the eye. Massive systemic doses are required to achieve effective intraocular tissue and fluid levels as a function of the magnitude of its ionization in the plasma and the significant degree to which it is protein-bound in the blood. For cases of intraocular infection of unknown etiology, penicillin should always be given in the presence of an agent active against gram-negative organisms.

STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

These antibiotics serve most widely in the treatment of tuberculosis, tularemia, and gram-negative bacterial infections due to sensitive strains and are particularly effective against Hemophilis influenzae, Klebsiella pneumoniae infections, and some strains of Proteus vulgaris. Occasional strains of Pseudomonas aeruginosa are nominally sensitive to streptomycin.

Absorption through the gastrointestinal tract is poor, and, accordingly, the intramuscular route is usually employed. Leopold and Nichols⁴⁶ found that systemic streptomycin in rabbits penetrated significantly into the extraocular muscles, conjunctiva, sclera, and aqueous humor but less adequately into the chorioretinal tissue and vitreous body. An appreciable increase in the concentration of the drug appeared in the secondary aqueous humor.

The most important side-effect of these drugs is a neurotoxicity which affects the eighth cranial nerve. Streptomycin, however, is essentially toxic to the vestibular function, causing impairment which is promptly recognized but for which the patient is able to compensate. Dihydrostreptomycin exerts a toxicity on the auditory system, and the development of deafness is often progressive after the cessation of therapy. Irreversible loss of hearing is a potential consequence even from small doses (1.0 to 5.0 gm.) and may occur within several weeks, or as long as six months may pass before any symptoms are manifest. Since streptomycin is basically as effective as dihydrostreptomycin and does not pose equally toxic complications, its selection is preferable to the latter.

TETRACYCLINES

The tetracyclines are bacteriostatic broad-spectrum antibiotics and have a considerable effect on gram-positive and gram-negative bacteria and, in addition, act against rickettsia and certain viruses. Chlortetracycline (Aureomycin), oxytetracycline (Terramycin), tetracycline (Achromycin, Panomycin) and demethylchlortetracycline (Declomycin) are evaluated conjointly, since tetracycline possesses the basic chemical structure of which all are comprised. These drugs were once preferred for the majority of penicillin-resistant staphylococcal infections as well as for penicillin-sensitized patients who had already experienced infections. However, the generally excessive use of these drugs has incremented both the prevalence and the danger of resistant strains of staphylococci, enterocci, and enteric gram-negative bacilli (*E. coli*, *B. proteus*, and *Pseudomonas aeruginosa*), and these consequences indicate the practicability of a more limited usage in the future.

Demethylchlortetracycline (Declomycin) is the most recently derived member of this family. It has been purported to afford two to four times the clinical potency of tetracycline and to provide more sustained blood levels than other tetracycline derivatives be-

cause of (a) the greater stability of the demethylated tetracycline in body fluids, (b) an implemented resistance to degradation, and (c) a lower rate of renal clearance.

The tetracyclines are readily absorbed from the gastrointestinal tract, and maximum plasma levels are attained within two to four hours and persist for six to eight hours. Solutions are also available for parenteral administration.

An estimation of the ocular penetration of these drugs has been conducted in several laboratories.^{35-37, 47, 48} It has been ascertained that elevated dosage levels favor their introduction to the tissues and fluids of the eye. The performance of Declomycin has not yet been appraised but a similar behavior would be expected.

The basic side-effects include nausea, vomiting, diarrhea, flatulence, loose stools, glossitis, stomatitis, proctitis, and vaginitis. Some patients experience a metallic taste in the mouth and the loss of olfactory acuity, and skin rashes occasionally have been aroused. The most troublesome consequence is diarrhea, which may be instigated by a direct irritative effect on the intestinal mucosa or an alteration of the bacterial flora. Sensitive strains of organisms are eradicated, permitting an overgrowth of resistant strains of staphylococci, coli, enterocci, and yeasts such as *Candida albicans*.

CHLORAMPHENICOL

Chloramphenicol was derived from *Streptomyces venezuela* in 1947 and is the first broad-spectrum antibiotic to be isolated and synthesized on a commercial basis. It is unique among natural compounds in that it contains a nitrobenzene group.

The drug has encountered considerable success in typhoid fever, the rickettsial diseases, and brucellosis. In medicine and surgery, it has been highly effective against staphylococci which are resistant to penicillin, erythromycin, and the tetracyclines and against gram-positive and gram-negative bacterial infections in patients sensitive to penicillin and the tetracyclines.

Chloramphenicol is available for oral or parenteral (sodium succinate) administration. It is promptly absorbed from the gastrointestinal tract, attaining maximum plasma levels within two hours. Significant plasma concentrations remain for six to eight hours, but the drug is rapidly excreted in the course of 12 to 18 hours. There is no effect on the intestinal flora, a feature dissimilar to the other broad-spectrum antibiotics. Oral administration is preferable to parenteral, and the intramuscular route does not provide substantially higher blood levels than oral doses.

Chloramphenicol has been extensively employed for intraocular infections as a function of its wide antibacterial spectrum and superior ability to penetrate the ocular tissues when given systemically.

The most adverse side-effect of this agent is the toxic influence on the bone marrow, due probably to the nitrobenzene moiety. Fatal blood dyscrasias have followed short-term as well as prolonged usage and, although the incidence of blood dyscrasia is low, the drug should not be used indiscriminately or for trivial illnesses. Blood studies should be conducted repeatedly during the course of treatment.

Special caution regarding dosages is advisable in the treatment of newly born or premature infants. Ostensibly normal doses have induced acute toxicity (the Gray syndrome) and death in a few infant patients.⁴⁹⁻⁵² The incapacity of the immature liver to detoxify the drug by glucuronide conjugation, combined with an incompletely developed renal function, results in an accumulation of the drug which reaches toxic proportions. The daily dose of chloramphenicol should not exceed 25 and 50 mg./kg. body weight in premature and full-term infants, respectively.

ERYTHROMYCIN

Erythromycin is a moderately broad-spectrum antibiotic but is most advantageously employed against gram-positive organisms (similar to the penicillin spectrum), es-

pecially penicillin-resistant staphylococci. The incidence with which coagulase-positive strains of *Staphylococcus aureus* are susceptible to erythromycin varies inversely with the prevalence of its use in any area. Where it has not been used excessively, approximately 75 percent of the strains are erythromycin-sensitive. Because organisms such as staphylococci quickly become resistant to erythromycin, it is advisable that it be used in conjunction with an additional agent (for example, bacitracin, chloramphenicol, or streptomycin). Cross resistance is almost complete to carbomycin.

Erythromycin is readily absorbed in the gastrointestinal tract. A more recent preparation, erythromycin propionate (Ilosone), exerts a more significant influence than the same dosage of oral erythromycin. In comparison, blood levels are elevated nearly threefold, and maximum concentrations are reached earlier and persist longer. Erythromycin for parenteral use is currently available. Intravenous or intramuscular forms of the drug, especially in maximally tolerable doses, have illustrated their penetrability with regard to the blood-aqueous barrier.⁵³ Quengesser and Ormsby⁵⁴ observed that it entered the aqueous humor in adequate concentrations when administered via the topical, subconjunctival, or intramuscular route.

Adverse reactions are uncommon. Nausea, vomiting, diarrhea, and skin rashes may occur, and overgrowth of monilia has also been noted.

OLEANDOMYCIN

The antibacterial spectrum of oleandomycin is similar to that of erythromycin. However, erythromycin is effective at a lower concentration and consequently is preferable for infections from organisms sensitive to both agents. Furthermore, a strain of staphylococci will occasionally be resistant to erythromycin and not oleandomycin.

The drug is currently marketed as triacetyloleandomycin (Cyclamen, TAO). This new form is claimed to be more rapidly and

completely absorbed from the gastrointestinal tract and to produce more elevated blood levels. Side-effects are not frequently encountered.

Oleandomycin enters the eye when given in massive doses, orally or intravenously. A single administration of 1,000 mg. successfully penetrates the aqueous humor of rabbits.⁵⁵ Dumas, Fielding, and Ormsby⁵⁶ have reported the phosphate form of the drug to penetrate the animal eye when applied locally, intravenously, and subconjunctivally. Subconjunctival injections were poorly tolerated, even in dosages as low as 2.5 mg./ml. and are therefore not recommended.

CARBOMYCIN

This drug has an antibacterial spectrum resembling erythromycin. Organisms gain resistance slowly, in the same fashion as their response to penicillin. Both erythromycin and oleandomycin are more active and potent than carbomycin, but there is nearly complete cross resistance between the three agents. The absorption and excretion pattern is also similar to that of erythromycin.

Carbomycin has been used topically in the form of the hydrochloride ointment to facilitate penetration of the aqueous humor.⁵⁷ It has been shown to cross the blood-aqueous barrier by oral, intravenous, or subconjunctival administration.⁵⁸

SPIRAMYCIN

This antibiotic has a narrow bacterial spectrum and resembles penicillin, erythromycin, and novobiocin in range of activity. Jones and Finland⁵⁹ considered it less active than erythromycin or oleandomycin.

The drug penetrates the eye when used locally, subconjunctivally, and orally, but requires the use of large doses.⁶⁰

It has been reported to be effective against toxoplasmosis in animals by Bogacz⁶¹ and Garin and Eyles.⁶² Investigations of patients with posterior uveitis, due possibly to toxoplasmosis, are currently being conducted at the Wills Eye Hospital.

NOVOBIOCIN

Novobiocin (Cathomycin, Albamycin) is a narrow-spectrum antibiotic which is most active against some strains of *B. proteus* and *Streptococcus fecalis*. Staphylococci rapidly develop resistance to novobiocin.

The drug is given orally and is usually well tolerated. The side-effects which have been reported include skin eruption, leukopenia, and a yellowish discoloration of the plasma—the product of a degradation process.

Novobiocin penetrates the ocular tissues poorly when given systemically unless the dosage is large. Intravenous administration in animals produced detectable levels following doses of 0.1 gm./kg. body weight,⁶³ and effective concentrations were obtained after subconjunctival doses of 12.5 mg.

RISTOCETIN

Ristocetin (Spontin) has an antibacterial spectrum similar to erythromycin and novobiocin, but is bacteriocidal rather than bacteriostatic. Staphylococci develop resistance to ristocetin very slowly and no cross resistance with other antibiotics has been demonstrated.

The drug must be given intravenously for the treatment of systemic infections. It is not absorbed from the gastrointestinal tract and intramuscular injection causes extreme irritation. The ocular penetration was evaluated in rabbits by Furguele, Sery, and Leopold.⁶⁴ No evidence of penetration in the presence of a normal or inflamed eye was demonstrated after intravenous doses of 50 to 100 mg./kg. body weight. Subconjunctival injection of 10 mg. produced irritation and also did not enter the eye.

In addition to the local irritation characteristic of the drug, several temporary but serious hematologic complications have occurred, among which have been neutropenia and acute thrombocytopenic purpura.

VANCOMYCIN

Vancomycin (Vancocin) is a bacteriocidal drug to which, at the present, most staphylo-

cocci are sensitive and which is especially effective against severe staphylococci-resistant infections. In addition, this drug has been successful against such gram-positive organisms as streptococci, pneumococci, enterococci, clostridia, and corynebacteria but not against gram-negative organisms. Thus the antibacterial spectrum is much the same as ristocetin. Resistance to the agent develops very slowly and no cross resistance has yet been demonstrated between ristocetin and other antibiotics.

Like ristocetin, vancomycin is not absorbed from the gastrointestinal tract, is irritating when given intramuscularly, and is administered by the intravenous route. The plasma concentration is thereby maintained for 12 hours, and, accordingly, two daily doses are sufficient. The drug diffuses well into the tissues but appears in the spinal fluid only when inflamed meninges have induced increased permeability.

Side-effects include chills, fever, and skin rashes and phlebitis at the site of injection. With extremely elevated blood concentrations, or levels greater than ordinarily produced, evidence of renal irritation and decreased auditory acuity has been noted. The drug should, therefore, not be selected for patients with impaired kidney function and both the kidney function and auditory acuity should be frequently examined in all patients.

No evaluation of ocular penetration has appeared in the literature. However, preliminary studies with rabbits are currently being conducted at the Wills Eye Hospital. This work has indicated that the drug does cross the normal blood-aqueous barrier after large intravenous doses and enters an inflamed eye with lesser doses.

Vancomycin should be reserved for serious infections caused by staphylococci or other organisms resistant to the more commonly used antibiotics.

NEOMYCIN

Neomycin is a powerful bacteriocidal antibiotic with a wide spectrum. It is active

against many gram-positive and gram-negative bacteria, including resistant staphylococci, streptococci, pneumococci, *Pseudomonas aeruginosa*, *B. Proteus*, *H. influenza*, and *Klebsiella pneumonia*. Among its advantages are the fact that resistance is not readily manifest by organisms and that it is not inactivated by exudates or enzymes. The drug has limited application for systemic use, however, because of its oto- and nephrotoxicity.

Neomycin has been extensively and advantageously employed in ophthalmology by means of local administration and subconjunctival injection.

Penetration of neomycin into the rabbit eye by local, subconjunctival and intraocular instillation was evaluated by Vogel, Leopold, and Nichols.⁶⁵ Studies by Sorsby and Ungar⁴⁰ disclosed that subconjunctival neomycin was effective against strains of penicillin-resistant staphylococci and *Pseudomonas aeruginosa* and ineffective against intraocular infections of *B. proteus*, although control of the latter could be obtained by prophylactic application of the drug. Subconjunctival doses of 500 mg. were tolerated, and elevated concentrations have been produced in the cornea and aqueous humor for 16 hours. The authors suggested subconjunctival neomycin (500 mg./ml.) to which is added epinephrine (0.25 ml. diluted 1:1000) as a standard method for the treatment of intraocular infections.

Neomycin is poorly absorbed from the gastrointestinal tract and, as a result, has been used for bowel asepsis. Intramuscular injection actuates a high plasma concentration but, because of renal impairment and irreversible damage to the eighth cranial nerve, is used only in critical situations. If the drug is given parenterally, the established average is 4.0 mg./lb./day in four doses and should not exceed 7.0 mg./lb./day or 1.0 gm. for 10 days.

We have seen several cases of hypersensitivity to the local application of neomycin on the conjunctiva or skin about the eye. Neomycin is employed widely in many oph-

thalmic preparations but, if the excessive and indiscriminate use of these preparations persists, more reactions and increased bacterial resistance will result. This development would be unfortunate because neomycin does have considerable value to the ophthalmologist at the present time.

KANAMYCIN

Kanamycin (Kantrex) is a bacteriocidal antibiotic which is closely related to neomycin and, to a lesser extent, to streptomycin. Its antibacterial spectrum is identical to that of neomycin, and a crossed resistance exists between the drugs. This drug also appears to be effective against some strains of tubercle bacilli resistant to streptomycin, isoniazid, and para-amino-salicylic acid, but resistance to kanamycin may be acquired during treatment.

Kanamycin, like neomycin, is negligibly absorbed from the gastrointestinal tract, and systemic treatment must therefore be implemented by the intramuscular route. Another similarity exists in the fact that parenteral use should be avoided except in the case of staphylococci or other infections which cannot be effectively treated with less toxic antibiotics.

Studies concerning ocular penetrability were performed in rabbits by Furgiuele, Sery and Leopold.⁶⁴ They found the drug to penetrate the normal eye satisfactorily when given subconjunctivally but inadequately by intramuscular injection, the latter method being favored by the presence of ocular inflammation. A 2.5-percent solution administered topically or 10 mg. subconjunctivally was well tolerated by the normal rabbit eye. For patients, the authors recommended large systemic doses to insure intraocular penetration.

Kanamycin also exhibits the toxic effect on the eighth cranial nerve produced by neomycin and streptomycin. Hearing loss, often severe, and irreversible deafness can occur with relatively small doses if renal function is impaired. The ophthalmologist can avoid

any toxic influence by the subconjunctival treatment of intraocular infections.

BACITRACIN

Bacitracin is a bacteriocidal antibiotic derived from a strain of *Bacillus subtilis* and has the same general spectrum as penicillin, with which it exhibits a pronounced synergism. Resistance to this antibiotic is rare, and its potency is not diminished by blood, pus, or necrotic tissue.

The drug is not absorbed from the gastrointestinal tract. When offered by intramuscular injection, bacitracin appears in tissues and pleural and ascitic fluid, but diffuses negligibly into the cerebrospinal fluid. It is excreted slowly, primarily by glomerular filtration.

Bacitracin is most frequently exercised in the topical therapy of infections caused by *Staphylococcus aureus* and other gram-positive bacteria, especially if the bacteria are resistant to other antibiotics. While parenteral application of the drug can induce kidney (tubular) damage, the condition is usually reversible. Systemic therapy has been limited to serious penicillin-resistant staphylococcal infections including meningitis and endocarditis. The intramuscular dose is 10,000 to 20,000 units, three or four times daily.

Bacitracin penetrates the ocular tissues by the subconjunctival route and can be instilled into the anterior chamber of the eye, the dosages for which are contained in Tables 2 and 3. For intraocular infections, it is most effective in combination with drugs such as streptomycin or polymyxin B which act against the gram-negative group of bacteria.

POLYMYXIN B

Polymyxin B (Aerosporin) is a potent bacteriocidal antibiotic and active against gram-negative bacilli, with the exception of many strains of *Proteus vulgaris* which are highly resistant. The drug is primarily favored in the treatment of *Pseudomonas aeruginosa* (*B. pyocyaneus*) infections.

This antibiotic is not absorbed from the gastrointestinal tract and hence, for systemic infections, is given parenterally. The intramuscular dose should not exceed 2.5 mg./kg. body weight per day for patients with normal kidney function. The plasma concentration decreases rapidly, but detectable blood levels persist for 12 hours—an indication that the drug be given in eight- or 12-hour intervals. There is no appreciable diffusion into the cerebrospinal fluid.

The factors which limit the use of polymyxin by the parenteral route in general medicine are a nephrotoxicity and the side-effects exerted on the central nervous system. Whereas nephrotoxicity is unusual in patients with normal renal function, proteinuria, hematuria, casts, oliguria, and nitrogen retention may occur in a certain number of patients, beginning on the fourth or fifth day of therapy. Other toxic manifestations include paraesthesias and numbness about the face, mouth, or extremities, lack of coordination, ataxia, dysarthria, and dysnergia. These symptoms, however, usually disappear when the therapy is discontinued.

Again the ophthalmologist gains the advantage of a potent antibiotic and avoids toxic complications by utilizing the subconjunctival route. Ainslie and Smith⁶⁶ have demonstrated that polymyxin E can satisfactorily penetrate the eye from subconjunctival sites. Polymyxin B also enters the ocular tissues in this manner and can be used in solution for intracameral injection or irrigation (tables 2 and 3).

SOFRAMYCIN

Soframycin is an antibiotic effective against many gram-positive cocci, especially staphylococci, and gram-negative bacilli. Lutz and Hofferer⁶⁷ observed that many strains of *B. proteus* and *Pseudomonas aeruginosa* were sensitive to the drug in vitro. Ainslie and Henderson⁴¹ found soframycin particularly suitable for subconjunctival antibiotic therapy. The drug was highly soluble in water, did not cause undue tissue irritation, and gained therapeutic concentrations in the

aqueous humor (in rabbits). Ainslie and Cairns⁴² reported satisfactory results for the subconjunctival treatment of corneal infections—both clinical and experimentally produced—caused by *Staphylococcus aureus* and albus, pneumococcus, *E. coli* and *Pseudomonas aeruginosa*. In the clinical study, a subconjunctival dose of 500 mg. was generally employed.

NYSTATIN; AMPHOTERICIN-B

Nystatin (Mycostatin) penetrates the eye inefficiently whether applied locally in solution or systemically. Experimental studies have provided some favorable evidence,^{68,69} yet the clinical response of mycotic keratitis to nystatin has not consistently reflected the promising results experienced by several authors.⁷⁰⁻⁷²

The drug is ineffective in the treatment of systemic mycotic infections because of poor absorption from the gastrointestinal tract and severe tissue irritation caused by injection.

Amphotericin-B (Fungizone) is also poorly absorbed from the gastrointestinal tract. However, the fact that it can be given intravenously has established it as the preferred agent for the treatment of systemic mycotic infections. Encouraging results have been obtained with amphotericin-B in the treatment of coccidiomycosis, histoplasmosis, cryptococcosis (torulosis), systemic moniliasis, and North and South American blastomycosis.

In the study by Montana and Sery,⁶⁹ no detectable levels of amphotericin-B were found in the aqueous humor of the normal rabbit eye after the drug had been applied topically, subconjunctivally, or intravenously. However, corneal infections with *Candida albicans* responded favorably to topical treatment with both amphotericin-B and nystatin and to the intravenous administration of amphotericin-B, if therapy was initiated within one or two days after inoculation. Thus there seems to be some penetration of the drug, at least into corneal tissue, with parenteral administration of the antibiotic.

Foster, Almeda, Littman and Wilson,¹⁵ using amphotericin-B with intraocular Volu-tella infections in rabbits and a single patient, estimated a safe dose to be 20 to 35 μ g./0.05 ml. intracamerally, 5.0 to 10 mg./gm. ointment topically, and 15 μ g. subconjunctivally. No aqueous humor penetration studies were performed. The authors considered that the amphotericin-B supplied to the patient via the intraocular, subconjunctival, and topical routes exerted a beneficial effect on the Volu-tella infection.

To minimize both the toxicity and side-effects (nausea, flushing, chills, fever, generalized pain, azotemia, and depressed cardiac conduction), the manufacturer of Fungizone (Squibb) recommends the following dose and method of administration for systemic infection: (a) the antibiotic to be given over a six-hour period every other day for a period of two to four months, (b) an initial adult dose of 0.4 mg./kg. body weight, increasing in subsequent infusions by increments of 0.2 mg./kg. until the level of maximum tolerance (1.0 to 1.5 mg./kg.) is attained, (c) each daily dose to be dissolved in 500 ml. of distilled water containing 25 gm. of glucose, to which may be added 2.0 to 4.0 mg. of heparin to prevent thrombophlebitis, and administered at a rate of 20 drops per minute.

COLISTIN

Colistin (Coly-Mycin) is a relatively new antibiotic which has been isolated from the bacteria *Aerobacillus colistinus*. It resembles the polymyxins in chemical composition and spectrum of activity. In vitro, a potent bacteriostatic and bacteriocidal action is manifest on a wide variety of gram-negative bacteria (*Coli aerogenes*, *Pseudomonas aeruginosa*, *salmonella*, *shigella*), but there is a lesser effect against *B. proteus*, fungi, and gram-positive bacteria (*staphylococci*, *streptococci*). Resistance to colistin has not readily occurred in vitro and no cross resistance to the present broad-spectrum antibiotics is known.

The activity of colistin is approximately

equal to that of polymyxin B but, as opposed to polymyxin, the clinical and laboratory experience to date have shown virtually no nephrotoxicity after recommended systemic doses. Ross, et al.,⁷³ found slight azotemia, but only in very young infants, and observed no other side-effects.

Two forms of colistin are available: colistin sulfate (Coly-Mycin S), a nonabsorbable form which has been used for bowel sterilization and topical medication, and colistin methane sulfonate (Colymycin M), the absorbable form which is employed parenterally and also subconjunctivally and topically. One mg. of pure colistin base has been assigned a potency of 30,000 units.

No detailed description has been published regarding the facility of ocular penetration but an investigation of this subject has recently been initiated at the Wills Eye Hospital. Schwartz and co-workers⁷⁴ referred to a study in which colistin was shown to penetrate the subretinal fluid in seven of 18 patients after an intramuscular dose of 33 mg. pure base. Gordon and McLean⁷⁵ successfully treated a *Pseudomonas* infection of the cornea with colistin eyedrops (500,000 units in 7.5 ml. sterile water) and two intramuscular injections (500,000 units). Subconjunctival injections (50,000 to 100,000 units in water) and solutions for intracameral irrigation (100,000 units per ml.) were estimated by the authors to be effective for the treatment of intraocular infections caused by *Pseudomonas aeruginosa*.

In man, single therapeutic doses of intramuscular colistin methane sulfonate promote high blood levels for eight to 12 hours. The dosage for systemic infections is 2.0 mg. of colistin base/kg. body weight per day, although as much as 7.5 mg./kg. body weight per day has been administered in critical situations without nephrotoxicity.

SULFONAMIDES

All the sulfonamides are essentially bacteriostatic and act against a variety of gram-positive and gram-negative bacteria. Except in the case of meningococci, the appropriate

antibiotic is superior to a sulfonamide drug for any given infection. The sulfonamides invariably act more slowly and less effectively than antibiotics, and their effect is curtailed by the presence of purulent material and bacterial products. Schneierson⁷⁶ found only a small percentage of isolated staphylococcal strains to be sensitive to sulfonamides in vitro.

The long-acting sulfonamides, sulfamethoxyypyridazine (Kynex, Midicel) and sulfadimethoxine (Madribon), have been introduced in recent years. Adequate blood levels of free drug are maintained with one or two daily doses, and the total requirement is less than that of the short-acting sulfonamides because of the reduced rate of renal excretion. Another new sulfonamide, sulfaethylthiadiazole, referred to also as sulfaethiodole (Sul-Spansion liquid, Sul-Spantab tablets), is conveniently available in a sustained released form to be given every 12 hours.

Most commonly used sulfonamides readily pervade the ocular tissues and fluids. Crabb, Fielding and Ormsby⁷⁷ noted therapeutic levels of sulfisoxazole (Gantrisin) in the aqueous humor of rabbits following topical and subconjunctival administration or injection. Since the blood-aqueous and blood-cerebrospinal fluid barriers are analogous, the study of the latter regarding the diffusion of sulfonamides in normal adults might be related to a similar behavior in the eye. Broger⁷⁸ found the presence of these drugs to be a function of both their plasma concentration and diffusibility, the latter acting as the limiting factor in the attainment of a therapeutic level. The accessibility of a group of these drugs to the cerebrospinal fluid was ranked in the following descending order: sulfamethazine, sulfadiazine, triple sulfapyrimidine mixture, sulfamerazine, sulfamethoxyypyridazine, sulfisoxazole, and sulfaethylthiadiazole.

All sulfonamides have the same range of therapeutic action and are characterized by a mutual cross resistance. The only advantages

of the long-acting sulfonamides over those whose effective duration is more limited are their convenience of administration and lower cost. A major disadvantage of the former is that the occurrence of a sensitization reaction may cause free sulfonamide to persist in the blood for a period of days.

Toxic and sensitization reactions such as drug fever, skin rash, blood dyscrasias, hepatitis, and Stevens-Johnson disease either have been encountered or are to be anticipated with the newer sulfonamides as well as the older ones.

FURALTADONE (ALTAfur)

This is the initial nitrofuran to have been effective orally in systemic bacterial infections. The in vitro bacteriocidal range of furaltadone (Altafur) includes both gram-positive and gram-negative bacteria: staphylococci (including antibiotic-resistant strains), streptococci, pneumococci, *C. diphtheriae*, *Clostridium* sp., *E. coli*, and other coliform organisms. The bacteria resistant to the drug include many strains of *B. proteus*, *Pseudomonas aeruginosa*, and *Aerobacter aerogenes*. The manufacturer claims that no cross resistance exists between this drug and antibiotics, and the development of resistance by sensitive organisms has not been observed.

Studies of the ocular permeability in rabbits by subconjunctival and oral administration are presently in progress at the Wills Eye Hospital. Preliminary results indicate extremely poor penetration of Altafur into the aqueous humor. It is soluble only at a highly acid pH, and the ocular tissues have been irritated as a result of subconjunctival injection.

The recommended daily dosage, given in four equally divided portions, is 22 to 25 mg./kg. body weight per day for infants and young children and 14 to 22 mg./kg. body weight per day for older children and adults, an average of one 250 mg. tablet four times a day with food. It is not advisable to continue the drug longer than 14 days.

A letter from the manufacturer (Eaton

Laboratories), dated July 1960, warned of the following side-effects:

1. *Neurologic.* Neurologic disturbances have been observed in 25 patients, of which two cases of ocular manifestations were reported in the literature.⁷⁹ Malfunctions of the eye included diplopia, extraocular muscle palsy, nystagmus, and blurred vision. Ten of the 25 patients with ocular disturbances also exhibited neurologic complications which included decreased auditory acuity, peripheral neuritis, dysphagia, slurred speech, and difficulty in phonation. The average duration of therapy prior to the onset of these disturbances was 38 days, and in all but one instance the symptoms disappeared without sequelae.

2. *Hematologic.* Thrombocytopenic purpura and neutropenia have been reported. Hemolytic anemia, primaquine-type, though not reported clinically, should be considered.

3. *Alcohol reaction.* Consumption of alcohol during Altafur therapy may cause a reaction characterized by erythema, urticaria, dyspnea, feeling of chest constriction, tachycardia, hypotension, bronchospasm, arthralgia, facial edema and nausea.

4. *Other responses.* Nausea, vomiting, gastric bleeding, and allergic skin rash have occurred.

MISCELLANEOUS ANTI-INFLAMMATORY AGENTS

In recent years, there has been an interest in the use of enzymes such as trypsin, chymotrypsin, streptokinase-streptodornase (Varidase)⁸⁰⁻⁸⁴ and also gamma globulin⁸⁵⁻⁹⁰ in combination with antibiotics for the treatment of severe infections.

The enzymes are presumed to remove the barrier substances such as fibrin and pus which accompany the inflammatory reaction and thus permit more effective contact of the antibiotic with the bacteria, enhance the action of leukocytes, and restore the free flow of blood and body fluids.

The action of trypsin has been attributed to a direct depolymerization of the fibrin

molecules. Streptokinase acts specifically on plasminogen to form plasmin which hydrolyzes fibrin, and streptodornase operates only on the nucleoprotein of dead cells. The role of pooled gamma globulin is supposedly mediated by the specific antibacterial antibodies which it contains, the antibodies acting to facilitate phagocytosis.

There has been no appraisal of the efficiency of these enzymes or of gamma globulin in the treatment of postoperative intraocular infections. Eareckson, Miller, and Long⁹¹ indicated that the local application of streptokinase-streptodornase as an eye bath, in conjunction with the use of polymyxin B, was beneficial in the treatment of a *Pseudomonas aeruginosa* corneal infection.

The doses for these anti-inflammatory agents are:

1. *Trypsin.* (a) Parenzyme aqueous or parenzyme in oil (National Drug): 5.0 mg. (1.0 ml.) intramuscularly, once or twice daily. (b) Parenzyme B (National Drug): one 5.0 mg. buccal tablet four times daily.

2. *Chymotrypsin.* (a) Chymar Aqueous (Armour): 0.5-1.0 ml. (5,000 units/ml.) intramuscularly, one to three times daily. (b) Chymar in Oil (Armour): 0.5 ml. (5,000 units/ml.) intramuscularly, one to three times daily. (c) Chymar Buccal (Armour): two tablets (50,000 units/tablet), four times daily.

3. *Streptokinase-streptodornase.* (a) Varidase (Lederle): 0.5-1.0 ml. (10,000 units/ml.) intramuscularly, twice daily; (b) Varidase (Lederle): drops (6,250 units of streptokinase and 1,250 units of streptodornase/ml. or 12,500 and 2,500 units/ml., a 125,000 unit vial diluted with either 10 or 20 ml. of sterile physiologic saline) topically, approximately four times daily. Since each of these agents is antigenic, the necessary precautions should be exercised.

4. *Gamma globulin.* (a) Sixteen percent solution, U. S. P.: 0.4 ml./kg. body weight, intramuscularly.

It should be emphasized that the primary success of this combination therapy is es-

pecially dependent on the choice of an antibiotic known to be effective against the bacterial pathogen.

SUMMARY

In our discussion of postoperative infections we have reviewed the etiologic microorganisms, cited the increase in the recognition of fungal pathogens, and discussed their incidence, potential sources, and means of prevention. Information was provided regarding the role of preoperative eye cultures and antimicrobial therapy.

Successful treatment of the active infection was described to depend upon the prompt use of the appropriate antibiotic and chemotherapeutic agent and the proper choice of that route of administration which would insure the accessibility of the drug to the in-

fected tissue and secure adequate concentrations. As a function of the frequency with which the responsible organisms remain unidentified, it was considered advisable to employ drugs with a broad antibacterial spectrum which could be given both subconjunctivally as well as systemically and in massive doses. If no improvement was observed within a period of 24 hours after the initiation of treatment, the substitution of other antibiotics in conjunction with systemic ACTH or corticosteroid therapy was recommended.

A listing of the individual antibiotic agents is contained in the accompanying tables which were designed to facilitate the selection of the most efficient drug, dosage and route of administration.

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RETINAL DETACHMENT SURGERY*

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Those fortunate enough to have served under Francis Heed Adler will never forget his keen critical analysis of the various problems he encountered. This concept of constant appraisal was indoctrinated in his students, and has led to this presentation.

During the past decade, there is no branch of ophthalmic surgery which has changed so radically as that employed for a patient with a retinal detachment. One frequently is asked, what procedure are you using now? To answer that question, and evaluate the results, the records of 100 consecutive patients were reviewed.

The pertinent statistics will be presented, though the main purpose is to review the failures and their possible causes. By this process, one may be able to avoid certain pitfalls, and perhaps save the sight of future patients.

STATISTICS

AGE

The age distribution of the patients is shown in Table 1. There are two interesting features to be noted: the three patients under 10 years of age were boys, all of whom had been hit in the eye some weeks or months previously, and had been considered cured until further examination revealed loss of vision due to a retinal detachment in the af-

fected eye; and the two patients over 80 years of age were aphakic, had retinal detachments occurring in their only seeing eye, and fortunately both were cured.

TRAUMA

Eight patients had direct trauma to the eye. Two of them had traumatic cataracts, and a retinal detachment was noted shortly following cataract surgery. One had an intraocular foreign body which was removed and subsequently his detachment also was cured.

It is always difficult to evaluate indirect trauma, since the possibility of compensation so frequently colors the patient's history. Three one-eyed myopic patients who developed symptoms within 48 hours of a rather severe blow on the head were adjudged as indirect traumatic detachments and were so reported to their insurance carriers.

TABLE 1

AGE DISTRIBUTION OF PATIENTS

Age (yr.)	No. of Patients
0-10	3
10-19	4
20-29	3
30-39	3
40-49	14
50-59	29
60-69	34
70-79	8
80-89	2
TOTAL	100

* From The Wills Eye and Lankenau Hospitals.

BILATERALITY OF DETACHMENTS

Twenty-three patients had bilateral detachments. Twenty of these had vision of hand movements or less in the uninvolved eye because of an old unoperated or unsuccessfully operated retinal detachment. There were four other one-eyed patients who had lost their vision (or their eye) for other reasons. This confirms the well-known fact that detachment of the retina frequently is a bilateral disease and every attempt should be made to save the eye that is first involved.

REFRACTIVE ERROR

Sixteen patients had more than 3.0D. of myopia, and 32 patients were aphakic. Ten of the aphakic patients were one-eyed because of unoperated or unsuccessfully operated retinal detachments in the opposite eye. Two of this group had had surgery for congenital cataracts in childhood.

TYPE OF SURGERY PERFORMED

A total of 125 procedures were performed by me on these 100 patients, 15 of whom had had one or two diathermy procedures before referral. Sixteen patients had intrascleral diathermy as a primary procedure—with or without the release of subretinal fluid—to close breaks alone, or breaks with a minimal amount of fluid. Fifteen were cured by this procedure and obtained 20/40 vision or better. One patient required a second scleroplastic procedure, which resulted in a cure.

Twenty patients had a primary scleroplastic procedure (scleral flap) with or without a silicone plate, but without an encircling tube. Of this group, 19 were cured, but three developed star folds in the macula and had less than 20/200 vision. The one failure was not cured by two scleroplastic procedures with encircling tubes.

A scleroplastic procedure combined with an encircling tube was my primary procedure on 64 patients. Sixteen patients had two procedures, three had three procedures, and one four procedures. One had a third procedure

performed elsewhere, and another a fourth and fifth procedure performed elsewhere, with anatomic reattachment of the retina finally being achieved. There may be other patients in this group who were later operated on elsewhere, although a six months' follow-up was achieved on every patient.

This type of procedure was used on the 15 patients previously operated on elsewhere for detachments, and on the one patient in whom a previous primary scleroplastic procedure had failed. It was used as my primary procedure in 30 of the 32 aphakic patients.

CAUSE OF FAILURE

One could probably classify all failures in retinal detachment surgery as failure to close the retinal break or breaks. In this group of 100 patients, there were 19 patients listed as failures. Thirty-two operations were performed on these patients. A few had only one procedure, and a second procedure was not advised, or was refused. I have attempted to list the causes of failure in rather broad categories:

POOR VISIBILITY

Five patients might be placed in this category. One aphakic patient with uveitis and keratitis; two with congenital cataracts, and a two-mm. opening in a dense capsule. (Both were operated "blind" with a complete encircling tube done in two stages. One has maintained 20/80 vision for a year, but elevation of the retina is still visible.)

Two others were aphakic patients with small round fixed pupils, and complete detachments.

SIZE OF THE BREAKS

One patient was a myope (-24D.) who was hit on the head by a large branch of a tree. He had numerous large holes, two to three discs diameters in size, all posterior to the equator, and the intervening retina appeared shredded. At operation an encircling tube with silicone plate appeared to

close all the breaks, but after two weeks the retina was completely detached, and the patient refused another operation.

The second patient presented a disinsertion from the 6- to 12-o'clock positions in the right eye, and the edge of the retina was curled posteriorly. A resection with encircling tube caught three fourths of the disinsertion and a second operation caught part of the remainder. Though the detachment did not progress, there was still elevation below, and a third procedure performed by Dr. Okamura succeeded in reattachment of the retina.

VITREOUS CONTRACTURE

Though a fair number of patients have evidence of vitreous contracture as manifested by star folds, equatorial folds, meridional folds, or fixed folds about the posterior pole, their presence certainly adversely affects the prognosis.

There were five patients in whom it was felt that the prime reason for failure might be ascribed to vitreous contracture. Four of them, all aphakic, had had previous detachment surgery, one with loss of vitreous during a scleral resection procedure. Definite breaks were obscured by the previous diathermy. One other patient who was phakic had also had previous surgery with rather marked vitreous contracture. It is not known whether this group had had any evidence of vitreous contracture prior to their primary surgery, which was performed elsewhere.

VITREOUS HEMORRHAGE

Two patients had a massive vitreous hemorrhage a few days following surgery. In one case it followed a primary procedure, and in one a secondary procedure. The ultimate result was satisfactory in one case, unsatisfactory in the other.

UVEITIS

Two patients had a severe uveitis, and had been treated for it before a detachment of the retina was noted. Both had definite cir-

cumcorneal injection and other evidences of uveal infection when referred for surgery. In both patients, the ophthalmoscopic examination was difficult because of posterior synechias and lens haze. In the one in which a break was recognized, a scleral buckle resulted in reattachment of the retina; the other was a failure.

OPERATIVE FAILURES

Though all failures might be considered as operative failures, the five cases in this category were considered as primarily caused by poor judgment or faulty surgical technique. Unfortunately, three were one-eyed patients who had lost their other eye from a retinal detachment.

One had a fairly large temporal break without extensive detachment. At surgery he was found to have an extensive staphyloma, involving most of the temporal wall of the globe. Subretinal fluid oozed from the minimal application of surface diathermy. A silicone plate with an encircling tube closed the break, but a second break developed which was not closed at a second operation, and the patient refused further surgery.

In two patients vitreous was lost in a secondary procedure. In one a large hole was not closed at the first operation, and I felt that my diathermy was too intense. He developed many fixed folds, and following a revision of his scleral buckle, I injected some vitreous and the eye became too firm and a necrotic area of sclera blew out, with vitreous loss and exposure of retina.

In the other patient, while completing a 360-degree encircling buckle, one end of the polyethylene tube slipped into the covered bed of the first resection. In attempting to push it back, excessive manipulation caused vitreous to be lost through the bed of the first resection. Two other patients had accessible tears about the size of the disc, both holes appeared closed at the time of surgery, but they developed massive vitreous retraction with ultimate complete funnel-shaped detachments.

DISCUSSION

Though the surgery of retinal detachments has undergone considerable change in the past decade, there are still many disappointments to those who perform this type of operation. Patients with a retinal break with no detachment, or minimal elevation of the retina, do very well with carefully controlled intrascleral diathermy. In this small series this accounts for 16 of the patients, one requiring a second procedure.

In all probability, at least half of this group might have been treated by light coagulation had it been available.

The advantage of the scleroplastic procedure with a silicone plate is that at the conclusion of successfully performed operation, one can visualize the treated choroid in contact with the break or breaks, and thus contact is maintained by the plastic plate and/or encircling tube. The procedure also reduces the vitreous volume, and may counteract the effects of vitreous retraction. Because of this mechanical forceful closure of the break, early ambulation is possible.

Another advantage of a scleroplastic procedure and applying diathermy under a scleral flap is that one deals with a layer of uniform thickness, less diathermy is required, and the sclera is not destroyed by diathermy.

It is difficult to define the criteria for using a scleroplastic procedure. It would be easier to say that in this series, intrascleral diathermy was used to close breaks without detachment or preclinical detachments. A scleral flap was prepared when there was a localized detachment with one break or two or three small breaks grouped together, and no other gross degenerative lesions. An encircling tube with or without a silicone plate under a flap was used as a primary procedure in 64 patients. This procedure was used in 30 of the 32 aphakics; in all myopes over $-3.0D.$; in all large or extensive breaks; for several breaks in different quadrants; and in all secondary or tertiary procedures.

One disadvantage of this procedure is that

it is time consuming, though this is of little consequence if it produces the desired result! Clinical impressions sometimes are not substantiated by statistics, though I feel I am seeing more patients who are anatomically cured who develop late macular changes, that is, small folds, cysts, or nondescript changes in the macula of unabsorbed edema. In a scleral-buckling procedure, the sclerotomy site or sites are closed before tightening the tube. There may be a small amount of residual subretinal fluid left, and with early ambulation in upper temporal quadrant detachments, this may gravitate toward the macula before absorption.

Prior to this technique, when several penetrating pins combined with intrascleral diathermy were used, and the patients kept bedfast for weeks, this phenomena seemed less prevalent—though at that time we were familiar with the syndrome of macular changes following detachment surgery. This may be more apparent than real, since the percentage of cures—especially of difficult cases—is greater with the buckling procedure.

Another cause of retinal edema and also of failure in the buckling procedure, especially if a wide buckle is used, is that with purse-stringing the globe, one gets small folds of retina on the buckle. Should such a fold connect with a break, fluid may pass over the dam to the posterior pole. This leak may eventually be sealed if the hole is closed with diathermy reaction, but in the interim fluid has spilled over, and will have to be absorbed. If enough fluid is present to prevent closure of the break, the operation is unsuccessful and will have to be repeated.

It is interesting to follow the evolution of scleroplastic procedures in retinal detachment surgery. First we had the scleral resection operation with its various modifications. At first it was used when conventional intrascleral diathermy combined with penetrating diathermy failed, or when experience led one to believe it would be un-

successful, that is, in high myopia, certain aphakic patients, and so forth. With this procedure came the realization that the application of diathermy to the choroid or thin scleral lamella in a resection had many advantages.

Following this, an attempt was made to counteract the unfavorable role the vitreous played in many patients with retinal detachments. Since in many cases the retina would not come in contact with the treated choroid, two methods of treatment evolved: one was the expanding school in which air or vitreous was injected into the posterior chamber to force the retina back against the choroid; the other the contracting school, which by means of plastic material, sutures, and so forth, reduced the volume of the posterior chamber and brought the diathermized choroid in contact with the retinal breaks. Undoubtedly, there is a place for both procedures.

The contracting school, having met with considerable success in difficult cases, naturally widened the scope of the operation until now in some instances it is used almost as a routine procedure. Its main advantage is that in an uncomplicated procedure, one can be almost assured the patient is cured when the operation is concluded. It may obviate the need of binocular bandaging, permits early ambulation, and reduces hospitalization to a matter of days. The disadvantages are that it can be technically difficult, and practically every surgeon without the experience of having operated on a large number of patients, runs into complications not mentioned in the published literature. The operation, though producing an anatomic cure, may appear too radical in some cases which experience has shown may be cured by less heroic measures.

The disadvantages of the use of penetrating and intrascleral diathermy are that an unnecessary amount of sclera is destroyed; iatrogenic breaks are not uncommon from

penetrating pins; and if failure occurs, the secondary procedure may be most difficult. The injection of air or vitreous into the posterior segment must certainly change the character of the remaining vitreous. This may be desirable, and one cannot be dogmatic as to its use or disuse.

An attempt has been made to analyze a small series of patients with retinal detachments, with especial reference to the failures. It is readily appreciated that I am essentially of the contracting school. In many of these patients there is so much at stake that one hesitates to try something with which he is not familiar, for example, a retinopexy with injection of air or vitreous in alternate cases. Unfortunately, the patients we see operated on by techniques different from our own usually are the other man's failures. We know nothing about the condition of the eye prior to surgery and can see only the end-result. We are also humbled by our own failures and cannot but wonder whether the end-result might have been more satisfactory had we done some things differently.

CONCLUSION

The treatment of a patient with a retinal detachment requires patience prior to and at the time of surgery. There are certain factors, such as poor visibility, large posterior breaks, and vitreous contracture, which complicate the operative procedure, and may lead to failure. Inadequate or excessive diathermy, inadequate drainage of subretinal fluid, and the loss of vitreous may result in failure, and are the results of faulty technique.

Fortunately, we have much more to offer the patient with a retinal detachment today than we had a decade ago. Let us hope that another decade will produce as many advances as the last one did.

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FRANCIS HEED ADLER

This *Festschrift* honoring Francis Heed Adler, was planned many months ago when he was still active as Professor of Ophthalmology in the University of Pennsylvania, School of Medicine, in anticipation of his elevation to Emeritus Professor. He was then also Editor-in-chief of the *A.M.A. Archives of Ophthalmology*. As we all know,

he served both posts with the utmost distinction.

His close friend, associate in clinical practice, distinguished colleague and successor as Head of the Department of Ophthalmology, Harold G. Scheie, was asked to undertake the difficult task of organizing this number of THE AMERICAN JOURNAL OF OPHTHALMOLOGY. As you see, he has done the

job superbly well. He invited the authors assembled here to contribute to this number and has spurred them on from time to time to meet the deadline. It is unnecessary to add that Dr. Scheie executed this commitment joyfully and with loyal affection and admiration for his chief, without Dr. Adler's knowledge.

It may seem strange to many of our readers that THE AMERICAN JOURNAL OF OPHTHALMOLOGY should go out of its way, so to speak, to honor the Editor of the *Archives of Ophthalmology*, which perhaps should have initiated its own *Festschrift* on the occasion. However, Dr. Adler was still its editor and his future regarding this post was not then foreseen. Since a *Festschrift* under these conditions could scarcely have been planned and carried through by the Staff of the *Archives* without his knowledge and acquiescence, an idea that would have offended his modesty, I thought that this great American ophthalmologist and editor should be given a special tribute and salute extolling him and his works in a dedicated number of THE JOURNAL.

Elsewhere in this issue are found his biography and the bibliography of his many contributions to scientific and clinical ophthalmology, which have forever beautified the face of ophthalmology. The many facets of this remarkable man are thus made evident by clothing the bare bones of eminent achievement with the flesh and blood of a warm and highly cultured personality of unyielding integrity.

Let us then consider particularly the editorial facet displayed by Francis Adler. I believe that it was Elbert Hubbard who said somewhere that "an editor is a person whose business is to separate the wheat from the chaff, and to see that the chaff is printed." This might apply to the common run of editors, but never to Editor Adler. Not only has he always discarded the chaff but also at times wheat that was good. He has only printed the best according to his sterling standards. This has made him a most formi-

dable figure in piloting American ophthalmic literature, and has led the *Archives of Ophthalmology* out of a slump to a peak of eminence and respect. His high standards have had great and good influence on the writings of all ophthalmologists, and this is not the least of his many achievements.

Here is an example of his sense of responsibility as an editor. In 1951 (Vol. 46, page 489) the paper by Eugene Schreck then of Heidelberg, Germany, on "The micro-organisms causing sympathetic ophthalmia" was published in the *A.M.A. Archives of Ophthalmology*. That his acceptance of this paper for publication worried Dr. Adler is attested to by the following editorial note over his signature. He said:

The importance of the conclusions drawn in the following paper ("the micro-organisms" etc., referred to) are obvious. If this work can be confirmed, the riddle of the causation of this dread disease will have been solved and the search for a preventative or a cure will have been put on a firm etiologial basis. *It is the policy of the Editorial Board of the A.M.A. Archives of Ophthalmology to publish only data which are well controlled* (italics mine). In our opinion this criterion has not been entirely fulfilled in this paper. For example, there are no control injections from non-sympathetic cases. This seems particularly important because of the author's suggestion that the organism may lie dormant in the extraocular tissues and be activated when it comes in contact with the uveal tissue.

The conclusions drawn by the author, particularly in connection with the use of antibiotics in eye injuries, are so important, however, that the article is being published at once to encourage comparable investigation by other workers.

As chief Editor of the *Archives* Dr. Adler gathered around him a distinguished Board which was active and loyal (vide John Dunnington's remarks) in support of his policies, and assisted him in the survey of contributions and the separation of the "chaff." One of his most wise decisions, I think, was the assembling of talented younger colleagues called "associates," like the Apostles, 12 in number, each of whom prepared at length a review article covering the annual contributions in the world's literature on some major division of ophthalmology. Each served a

specified term, to be replaced by others. Any one who has tried his hand at the preparation of such a review article is painfully aware of the difficulties and time-consuming work required. At the same time on the conclusion of the task, he will realize that he has had a fine experience and a remarkable increment in his scientific knowledge. These 12 reviews a year have been of the greatest value to ophthalmologists.

Under Editor Adler's reign the *Archives* has reached a very high place as a scientific journal. With the remarkable growth of experimental ophthalmology in the United States, particularly in the last 15 years, our residents and younger ophthalmologists are inoculated with scientific thoughts and techniques. The influence of the writings and editorial activities of Francis Adler on this burst of exciting activity has been widely felt. But the pleasures and intellectual rewards of clinical practice have likewise found some expression in the pages of the *Archives*, giving comfort particularly to the older generation of ophthalmologists, most of whom find utmost difficulty in understanding what the younger generation is talking about. Editor Adler maintained a good balance in his pages in this respect, for as John H. Dunnington said in his presidential address, "Interdependence" before the Academy of Ophthalmology and Otolaryngology in 1959 (Tr. Am. Acad. Ophth., 64:7, 1960):

A few years ago the scientist remained aloof in his laboratory, shielded from the outside world by the abstruseness of his observations. From his ivory tower emerged scientific facts of incalculable value, yet they often fell on deaf ears, for between the scientist and the clinician there was no common ground. Each was distrustful of the other and each pursued his own course with selfish pride, unconcerned with the problems of his fellow worker. Today, this mutual lack of appreciation has largely disappeared and both work together in the solution of difficult medical problems.

Dr. Adler through his work has done

much to bring the laboratory and clinic into closer rapport.

His successor as chief Editor of the *Archives*, David G. Cogan of Boston, is a wise clinician, a superb laboratory scientist, and administrator of the influential Howe Laboratory. What better choice could have been made to succeed Francis Adler? Under Dr. Cogan's term of office, the fulfillment of the promise of onward and upward progress of the *Archives* is assured.

The editors of the two leading ophthalmic journals have of course been rivals. But Adler and Vail have been the friendliest of rivals and have had many happy hours of companionship together. There have been "gentleman's agreements" that were scrupulously kept. My regret is that we have not played our violins together, but Dr. Adler is a violinist and I am a fiddler. His bowing and technique are far better than mine but I like to think that my "tone" surpasses his. There is a great spread between "Love in Bloom" and a Beethoven violin concerto. Perhaps that is why we have never gotten together with our violins (fiddles).

But each of us in his own way has striven to be good editors, and if the "bowing" of the *Archives* is more austere, the "tone" of THE JOURNAL is mighty good. The *Archives* and THE JOURNAL supplement and complement each other and there will always be room for both in ophthalmic literature. With Adler on THE JOURNAL and Cogan on the *Archives* we can't lose.

J. G. Saxe in 1855 said,

Who would not be an editor?

To write the magic *we* of such enormous might,
To be so great beyond the common span.

It takes the plural to express the man.

It has indeed taken the plural to express our thoughts of Francis Heed Adler.

So to him our salutes and hearty good wishes.

Derrick Vail.

ABSTRACT DEPARTMENT

EDITED BY DR. F. HERBERT HAESSLER

Abstracts are classified under the divisions listed below. It must be remembered that any given paper may belong to several divisions of ophthalmology, although here it is mentioned only in one. Not all of the headings will necessarily be found in any one issue of the Journal.

CLASSIFICATION

1. Anatomy, embryology, and comparative ophthalmology
2. General pathology, bacteriology, immunology
3. Vegetative physiology, biochemistry, pharmacology, toxicology
4. Physiologic optics, refraction, color vision
5. Diagnosis and therapy
6. Ocular motility
7. Conjunctiva, cornea, sclera
8. Uvea, sympathetic disease, aqueous
9. Glaucoma and ocular tension
10. Crystalline lens
11. Retina and vitreous
12. Optic nerve and chiasm
13. Neuro-ophthalmology
14. Eyeball, orbit, sinuses
15. Eyelids, lacrimal apparatus
16. Tumors
17. Injuries
18. Systemic disease and parasites
19. Congenital deformities, heredity
20. Hygiene, sociology, education, and history

3

VEGETATIVE PHYSIOLOGY, BIOCHEMISTRY, PHARMACOLOGY, TOXICOLOGY

Hockwin, O. and Weigelin, E. **A method for determining the concentration of butazolidin in the human aqueous after peroral administration.** Arch. f. Ophth. 12:133-136, 1960.

The authors' study shows that it is probable that the concentration is increased with intraocular inflammation and possibly the age of the subjects influences the butazolidin-concentration-gradient between, plasma and aqueous. (2 figures, 1 table, 9 references) F. H. Haessler.

Hofmann, H. and Lembeck, F. **Experimental study of the mechanism of action of zonolytic ferments.** Arch. f. Ophth. 162:111-119, 1960.

The authors made microscopic studies of the tearing of zonula fibers as a result of increased tension and also with the addition of enzymes. They confirmed previous observations that enzymatic zonulolysis can only take place in fibers under tension. The fibers differ from other ocular tissues in that they undergo almost no

enzymatic change through trypsin or alphachymotrypsin. As an explanation for the limitation of activity of the enzymes to zonula fibers under tension the authors assume that intramolecular structural changes occur in the proteins of the fibers. (3 figures, 14 references)

F. H. Haessler.

Laue, H. **The latent period (retino-thalmo-cortical) in the rabbit of stimulation with equal-energy varicolored light.** Arch. f. Ophth. 162:205-214, 1960.

Stimulation of rabbits' eyes with lights of equal energy and from various spectral regions showed that it was only with red light (λ max 641 m μ) that no electroretinogram and no specific action potentials of the lateral geniculate body and the cortex could be derived. Similar latent periods of the eye and brain action potentials were found in spectral regions of shorter wave length—blue, green, and yellow. The fact that individual stimuli of equal energy in a spectral region greater than 600 m μ do not give rise to action potentials suggests that red light gives rise to a visual impression in the rabbit. (7 figures, 20 references) F. H. Haessler.

Lembeck, F. and Hofmann, H. **Experiments in inhibition of enzymatic zonulolysis.** Arch. f. Ophth. 162:120-123, 1960.

When using enzymatic zonulolysis in cataract extraction the enzyme solution usually disappears from the anterior chamber during the surgical procedure. However, when high concentrations are used it is occasionally desirable to use an experimentally tested inactivator. The authors found that in the ox eye Kallikrein-inactivator slightly inhibits the zonulolytic action of trypsin and that the soybean inhibitor does so greatly. The latter can be injected into the anterior chamber of the eye of the rabbit without causing any irritation whereas the Kallikrein-inactivator is injurious. If the soybean inhibitor is injected into the anterior chamber of the rabbit eye one minute after the injection of a quantity of trypsin or alphachymotrypsin, enzyme injuries can be prevented.

These experiments provide data which can be useful in the management of zonulolysis in the human eye. (1 table, 3 references) F. H. Haessler.

Müller, H. K., Hockwin, O. and Kleinfeld, O. **The determination of pilocarpine in the human aqueous by polarography.** Arch. f. Ophth. 162:107-110, 1960.

The authors have recently shown that the ability of the lens to absorb oxygen from a nutrient solution can be reduced or completely inhibited by the addition of pilocarpine. They now describe a method for determining the pilocarpine content of the aqueous by means of polarographic adsorption-analysis. (3 figures, 1 table, 4 references) F. H. Haessler.

Rehak, S. and Vrana, M. **Volumetric rheometry: a new method for measuring the facility of aqueous outflow in experimental animals.** Ophthalmologica 139: 393-400, May, 1960.

The principle underlying the authors'

method is this: by means of a 24 gauge cannula and a cardiac catheter, the eyes of anesthetized rabbits are connected with a perfusion system designed for continuous observation of pressure and displaced fluid. A starting level for the perfusion is established at the eye's own (physiologic) pressure P_0 . Then 50 μ l of saline solution are injected into the eye (anterior chamber) within 30 seconds and "held" there for five minutes. The intraocular pressure rises sharply during the injection and then drops gradually as aqueous is expelled through the outflow channels. At the end of the five minutes the initial pressure (P_0) is restored which causes some backflow of fluid from the anterior chamber into the perfusion system. By subtracting the amount of this backflow from the 50 μ l injected the authors obtain the amount of fluid which escaped through the outflow channels of the animal. Dividing this by the average of the observed pressure and by time yields C, which is the coefficient of the facility of aqueous outflow.

The average values for C and F (rate of aqueous flow) in rabbits with normal P_0 (19.7 mm. Hg) were 0.251 and 2.6 respectively. In a number of rabbits P_0 was found to be elevated to an average of 35.7 mm. Hg which the authors attribute to the cannulation. In these rabbits C was 0.290 and F 7.62. The facility of outflow increased somewhat after the death of the animal. (2 figures, 13 references)

Peter C. Kronfeld.

Schrader, K. E. **Orisul concentration in the vitreous after oral application.** Klin. Monatsbl. f. Augenh. 136:855-859, 1960.

Orisul (Ciba) is a sulfonamide. Patients scheduled for enucleation received the drug prior to surgery. The vitreous was analyzed post-operatively and the Orisul concentration measured. The study revealed that application of three grams of the drug within 24 hours yields a thera-

peutically effective concentration. However, if six grams are given within four days there is evidence of optimal bacteriostatic concentration of Orisul in the vitreous. (1 figure, 14 references)

Gunter K. von Noorden.

Shackel, B. and Davis, J. R. **A second survey with electro-oculography.** Brit. J. Ophth. 44:337-352, June, 1960.

Electro-oculography (EOG) is the measurement of the potential difference between the front and back of the eyeball. This potential difference is measured on the eyeball with known rotations, by the use of peri-orbital electrodes. EOG is relatively stable for long periods of time. No general diurnal pattern for EOG fluctuations was found. A general distribution was found for vertical-movement potentials and the relation between vertical and horizontal movements was evolved. (2 figures, 4 tables, 15 references)

Irwin E. Gaynon.

Sobanski, J. and Swietliczko, I. **Influence of ocular and cerebrospinal fluid pressure on the diastolic blood pressure of the central retinal vein.** Klin. Monatsbl. f. Augenh. 136:791-794, 1960.

The diastolic blood pressure of the central retinal vein is influenced by the cerebro-spinal fluid pressure acting upon the vessel during its course through the optic nerve. Spinal puncture results in decreased diastolic pressure of the central retinal vein. Paracentesis leaves the diastolic retinal vein pressure relatively unaffected, while the intra-ocular as well as systolic and diastolic retinal artery pressures are lowered by this procedure. (1 figure, 10 references)

Gunter K. von Noorden.

Witmer, R. and Bühler, E. **Immune electrophoresis of the lens.** Arch. f. Ophth. 162:193-204, 1960.

The authors show that the human lens

has at least three or four proteins in common with the lens of mammalian eyes but that on the other hand it has one protein fraction belonging to a crystallin which is specific only for man. (5 figures, 31 references)

F. H. Haessler.

4

PHYSIOLOGIC OPTICS, REFRACTION, COLOR VISION

Aznarez Garcia, Jose, and Del Pilar Aznarez Cocho, Maria. **A cause of asthenopia which has been but little investigated.** Arch. Soc. oftal. hispano-am. 19: 983-986, Dec., 1959.

The author believes that an inadequate amplitude of fusion accounts for symptoms of asthenopia encountered in patients with normal or properly corrected refraction and normal binocular muscle function. In such cases examination on the synoptophore revealed a narrow fusion amplitude, usually less than five degrees of convergence, and less than three degrees of divergence. Several days of exercises on the synoptophore, widened the fusion amplitude and led to the disappearance of the previously resistant symptoms of asthenopia. The author believes that neurotics are prone to have exaggerated symptoms of asthenopia and that the impressive effect of the instrumentation and exercises may be a beneficial psychologic factor which also contributes to the relief of their asthenopic symptoms.

Ray K. Daily.

Bending, G. C. **Current status of intra-ocular acrylic lenses.** Canad. M. A. J. 83: 174-175, July 23, 1960.

This is a general review aimed, presumably, at the general practitioner. No new material is presented. Because of the relatively high incidence of complications, the author concludes that the Ridley posterior-chamber lens has proved unsatisfactory. He states that figures on the anterior chamber lenses are not available

but that the results reported thus far are encouraging. Lawrence T. Post.

Verdaguer, Juan. **The euthiscope in the treatment of amblyopia.** Arch. chil. de oftal. 16:15-23, Jan.-June, 1959.

The author reviews briefly the modern approaches to the problems of amblyopia and discusses the use of the visuscope and the euthiscope in Cueppers technique. He describes a series of sessions with the euthiscope and concludes that this type of treatment is helpful in cases of amblyopia with foveal fixation, with erratic fixation, and with paracentral fixation not very far from the fovea. Even in these cases a great deal of cooperation is required from the patient and the parent; a large number of sessions, between 50 and 110, is needed to obtain any results. However, the author feels that this is the first progressive approach to ambliopias, which until recently were ignored as insurmountable problems. (5 figures, 12 references) Walter Mayer.

Vidal, Sergio. **High myopia in an homologous premature twin.** Arch. chil. de oftal. 16:11-14, Jan.-June, 1959.

The author briefly reviews retrolental fibroplasia in premature babies. He notes that high myopias are frequently found in premature babies who had an incomplete retrolental fibroplasia. This myopia frequently is near 10 diopters and usually remains unchanged during the first decade of life. The author describes two homologous premature twins, one of which weighed 1900 grams and the other 1300 grams; the first stayed in the incubator less time than the second one and always has been a stronger and taller baby. The heavier one of the two had a two-diopter hyperopia, whereas in the smaller baby a myopia of more than eight diopters was manifest before it was one year old. The author feels that this is a definite proof that high myopia is the re-

sult of extragenetic factors, in this case an attenuated form of retrolental fibroplasia. (8 references) Walter Mayer.

5

DIAGNOSIS AND THERAPY

Arruga, Alfred. **The value of a Gluck's metallic post-operative eye shield.** Brit. J. Ophth. 44:381-382, June, 1960.

On the first postoperative day a cataract patient elected to leave her bed. She struck her head against a door and received a laceration above the brow and an iris prolapse. The shield was badly dented and without it she would have probably lost the eye. (4 figures)

Irwin E. Gaynon.

van Beuningen, E. G. A. and Edler, G. **Colored stereo-photography of the chamber angle.** Klin. Monatsbl. f. Augenh. 136:816-818, 1960.

Satisfactory pictures are obtained with a slitlamp attachment manufactured by C. Zeiss. (6 figures, 5 references)

Gunter K. von Noorden.

Gormaz, A. and Eggers, C. **Experiences obtained with 75 keratoplasties.** Arch. chil. de oftal. 16:54-65, Jan.-June, 1959.

The authors review fairly extensively the indications for lamellar and penetrating corneal transplants. They describe in detail their techniques in each one of these two types of keratoplasty and analyze the results they have obtained in 75 patients. A discussion of the complications which appeared is extensive and suggestions are given as to how to improve the prognosis in this type of surgery. (27 references) Walter Mayer.

Krabisch, H. and Seidel, K. H. **Contributions to fundus photography with an ophthalmoscope after Thorner.** Klin. Monatsbl. f. Augenh. 136:818-821, 1960.

A device for fundus photography consisting of an ophthalmoscope (model Thorner) connected with an Exakta

Varex camera is described. This relatively simple apparatus permits fundus photography for the practicing ophthalmologist without investment in more complicated and expensive equipment. (3 figures) Gunter K. von Noorden.

Lijo Pavia, J. **Alphachymotrypsin retrobulbar in the treatment of intra-ocular hemorrhages.** Rev. oto-neuro-oftal. Sudam. 34:68-69, Oct.-Dec., 1959.

The author has used retrobulbar alphachymotrypsin in the treatment of intra-ocular hemorrhage of various origin and obtained good results in 12 of his 14 cases. He first gives 500 units and increases the dosage to 800 or 1000 units at weekly intervals. (3 figures, 3 references)

Walter Mayer.

Mann, Ida. **Experimental treatment of Australian trachoma with special reference to Lederkyn.** Brit. J. Ophth. 44:324-336, June, 1960.

Lederkyn (Midicel) is a slow-acting relatively non-toxic sulfa drug. Lederkyn acts by killing the virus. The dosage in children over the age of six years is one tablet per day for two weeks. Where it is administered in school, three tablets may be given on Friday.

At the end of two weeks the hyperemia is less and the discharge has cleared. After four weeks the tarsal plate is smoother, the follicles are flat and are still visible. The follicles are converted into scars by the ninth month. Corneal changes are more rapid. Edema clears after three weeks and gradually the vessels clear. "Treatment of the most severe cases may yield surprisingly good results even when the pannus has covered the pupillary area." (2 tables)

Irwin E. Gaynon.

Matthäus, W. **Experiments with improved fundus photography.** Klin. Monatsbl. f. Augenh. 136:821-825, 1960.

An attachment was developed which, when connected with the Exacta Vera camera, yields fundus photographs. (8 figures, 3 references)

Gunter K. von Noorden.

de Saint-Martin, R. **Advantages of a scleral prosthesis after enucleation.** Ann. d'ocul. 193:650-658, Aug., 1960.

An unusual implant after enucleation of the globe is described. An eye that has served as a donor for corneal transplantation is cleansed and the contents completely removed. The original insertions of the rectus muscles are marked and into this empty scleral shell an acrylic implant is placed. The opening where the cornea was excised is then closed. After enucleation this prepared scleral shell with its implant is placed into Tenon's capsule and the rectus muscles are sutured to the sclera at the marks previously made. Tenon's capsule and the conjunctiva are then closed over this implant. The author states that this gives good restoration of the volume of the globe and provides excellent motility. (9 references)

David Shoch.

Siebeck, R. and Wallensack, J. **Eye findings in spontaneous unilateral carotid thrombosis.** Klin. Monatsbl. f. Augenh. 136:852-855, 1960.

The case of a 55-year-old patient is reported. Symptomatology and diagnosis are discussed. (5 references)

Gunter K. von Noorden.

Smith, Redmond. **A new technique for opening the canal of Schlemm.** Brit. J. Ophth. 44:370-373, June, 1960.

The author describes his technique of gaining access to the canal of Schlemm by an ab externo approach. A three-millimeter incision is made at the limbus under microscopic control. The canal is entered and a fine nylon suture is then introduced and threaded just less than one quarter of the circumference. A new

incision is then made at the two-o'clock position. The nylon suture is reintroduced and brought out through an incision made at the four-o'clock position. The suture is now drawn taut and it appears in the anterior chamber after having burst through the antero-medial wall of the canal of Schlemm. (9 figures, 2 references)

Irwin E. Gaynon.

Verdaguer, J. **Indications for steroid therapy.** Arch. chil. de oftal. 16:82-88, Jan.-June, 1959.

The author feels that Wood's use of steroids only when the causative agent of an intraocular inflammation has been identified is impractical, considering the very few cases in which an agent can be isolated, and the gravity of many of these conditions. He calls attention to the dramatic effect obtained with steroids in many of these cases in which, if there is any danger of a tuberculous infection, the treatment may always combine proper specific antituberculous therapy with steroids. He then presents several case reports of optic neuritis, acute choroiditis, metaherpetic infections and central serous retinitis in which he has used steroids with great success. Walter Mayer.

Weekers, R., Prijot, E., and Lavergne, G. **Measurements of the ocular tension, the resistance to aqueous outflow and the ocular rigidity in exophthalmos of endocrine origin.** Ophthalmologica 139:382-392, May, 1960.

In the diseases comprised under the term "endocrine exophthalmos," the attempt to look up or the actual looking-up may cause a marked temporary rise in ocular tension. This may be misinterpreted as a sign of chronic simple glaucoma or may lead to false estimates of the ocular rigidity and of the facility of aqueous outflow (cfr. Am. J. Ophth. 36:1286, 1953). (10 figures, 9 references)

Peter C. Kronfeld.

6

OCULAR MOTILITY

Cortes, Mario. **Paralysis of the superior oblique muscle.** Arch. chil. de oftal. 16:25-31, Jan.-June, 1959.

The author presents a case of paralysis of the right superior oblique muscle. He discusses the differential diagnosis between paralysis of the superior oblique muscle in one eye and paresis of the superior rectus muscle of the other eye and points out the great practical importance of Bielschowsky's maneuver for this differential diagnosis. In treatment the author feels it is more reasonable to reinforce a paretic muscle than to weaken a perfectly normal muscle. In this case a tucking of the paretic superior oblique muscle was done with fairly good cosmetic results. (4 figures, 21 references)

Walter Mayer.

Matteuci, P. **Motor difficulties in the strabismic amblyope.** Ann. d'ocul. 193:641-649, Aug., 1960.

The author pays his respects to the theory of the sensory origin of strabismic amblyopia, but feels that almost all of these cases are of a sensori-motor origin. He states that in those patients with amblyopia with strabismus, monocular fixation is central and generally spatial localization is exact. It is only when a motor anomaly is added to the sensory dysfunction that a true strabismic amblyopia results. He further adds that in almost all cases of strabismic amblyopia there is a hand-eye incoordination which would indicate the existence of further sensori-motor difficulties. (4 figures, 21 references)

David Shoch.

Piper, H. F. and Holland, G. **Clinical and electrographic viewpoints in the evaluation of ocular paralysis and nystagmus.** Arch. f. Ophth. 162:137-165, 1960.

This discussion is based on detailed studies of 23 patients, each of which is

summarized extensively. The authors assume that one finds a hyperkinetic nystagmic and a hypokinetic-paretic factor in every disturbance of gaze. The electro-oculographic method makes it possible to register the patterns of various components of the patterns of behavior of the pair of eyes in motion. In a first group of six cases the patients present a predominantly hypokinetic form of acquired abnormality. In a second group of five patients the predominantly hyperkinetic disturbance was ascribed to labyrinthine or cerebral disturbance. In two further groups the patients had congenital anomalous pattern of motility. (11 figures, 33 references)

F. H. Haessler.

Sachsenwanger, R. **The variability of the apparent angle of squint.** Arch. f. Ophth. 162:166-177, 1960.

The angle of squint was measured photographically in 1,339 subjects. The causes for the apparent position of the eyes were considered and various eye-types emerged. It was found that the magnitude of the apparent angle of squint has a statistically reliable relationship to the refraction. Eyes with myopic changes in the fundus have a smaller average angle than other myopic eyes. In the course of the first three decades the average size of angle decreases; after that a constancy of average value becomes manifest. There is no correlation between corneal refraction and apparent angle. (12 figures, 15 references)

F. H. Haessler.

Sünderhauf, A. **Investigations regarding the regulation of ocular movements.** Klin. Monatsbl. f. Augenh. 136:837-852, 1960.

Eye movements were studied by means of a sensitive photographic-registration method. Discrepancies between the smooth and almost instant muscular response during pursuit movements, and the estimated transmission time which

such a response must take if the reflex path includes the occipital cortex, led the author to believe that precortical reflex arcs must exist in addition to occipital cortical regulatory centers. Such mechanisms could be provided for by proprioceptive impulses from the extraocular muscles to the motor nuclei. (13 figures, 4 tables, 41 references)

Gunter K. von Noorden.

7

CONJUNCTIVA, CORNEA, SCLERA

Charlin, C. **Muco-cutaneous-ocular syndrome.** Arch. chil. de oftal. 16:150-155, July-Dec., 1959.

The author describes his experience with two cases of Stevens-Johnson syndrome in which a restoration of the cul-de-sacs was done with labial mucosa. He feels that in severe corneal involvement a keratoplasty may be indicated. The author suggests that the incidence is increasing and that it is not an isolated disease. It may appear as a complication of rheumatic fever, pneumonia or malaria. (2 figures, 6 references) Walter Mayer.

Dark, A. J. and Thomson, D. S. **Lattice dystrophy of the cornea. A clinical and microscopic study.** Brit. J. Ophth. 44:257-279, May, 1960.

A full ocular history of two families suffering from lattice type dystrophy of the cornea is presented in some detail. One family is covered for six generations and the other for four. All available members of the two unrelated families were seen and examined thoroughly and in one person a histologic study was made of the cornea and of a cartilage biopsy. A total of 121 members was examined of whom 16 were found to be affected and one of them had transmitted the disease directly to four of her children; it is of interest that in one family the disease appeared around the age of 45 years and in the

other the age was 35. In all of the subjects the signs and symptoms were about the same and were typical of the disease.

The dystrophy affects the anterior layers of the substantia propria which is the primary site of the disease. It is not impossible that it represents a local manifestation of a general disease even though this histologic study of the cartilage of a patient showed no irregularities. The microscopic studies indicated that within the stroma the affected component is the collagen ground-substance rather than the nerve fibers or the keratoblasts. Staining fibrils were found within the collagen and the amorphous material deposited within the stroma was shown histochemically to contain mucopolysaccharide and fluorescent protein. The epithelium, Descemet's membrane and the endothelium were found to be quite normal. (13 figures, 27 references) Morris Kaplan.

Espildora-Luque, C. **Conjunctival aneurysms in diabetes.** Arch. chil. de oftal. 16: 125-127, July-Dec., 1959.

The author was interested in finding out whether conjunctival aneurysms are more frequent in diabetics and if they are related in frequency to the retinal aneurysms or to the severity of the diabetic retinopathy. He made several studies comparing different types of diabetics and control individuals and reached the following conclusions. The conjunctival aneurysm is not related in any way to the diabetes, to the retinopathy, or to the generalized vascular disturbance encountered in diabetes. The increased incidence of conjunctival aneurysms found in diabetics as compared to control patients seems to be in direct relation to the number of these patients who also have hypertension. It is noteworthy that conjunctival aneurysms in control patients without diabetes occurred only in the controls who were hypertensives. (3 references)

Walter Mayer.

Mann, Ida. **Investigation of the sources of trachoma in the white school population of western Australia.** Brit. J. Ophth. 44:321-323, June, 1960.

The incidence of trachoma seems to be increasing; 58 percent of the native population and 4 percent of the Caucasians are afflicted. Of 246 cases of trachoma in white children, 115 were in immigrants, mainly Italian, and some Poles and Jugoslavs. Trachoma is still endemic in some areas in the white population with neither native nor immigrant contacts.

Irwin E. Gaynon.

Mullins, M. M. **Keratomalacia associated with adrenal hypoplasia in a defective.** Brit. J. Ophth. 44:300-305, May, 1960.

The condition of xerosis may vary from a mild conjunctivitis to a severe keratomalacia and is seen most frequently in male babies with malnutrition or avitaminosis. Mullins describes a one-year-old boy with extreme malnutrition due to insufficient sucking reflex which in turn was thought to be due to mental deficiency but was later proved to be due also to adrenal hypoplasia. The infant seemed unable to eat and soon developed, with other marasmic signs, marked keratomalacia of each eye which resulted in rupture of each cornea with rapid degeneration of the eyeball. Treatment of the eyes or the whole infant was of no avail and after death autopsy revealed very small hypoplastic adrenal glands. (10 references)

Morris Kaplan.

Olivares, M. **Treatment of herpes simplex of the cornea.** Arch. chil. de oftal. 16: 5-8, Jan.-June, 1959.

The author reviews the pathologic findings in dendritic keratitis and the metaherpetic type of keratitis. He then points out the similarity between a keratitis neuroparalytica and the metaherpetic keratitis. In the former the main problem

is the decrease or absence of corneal sensitivity, and therefore protection of the epithelium is the treatment of choice. Considering the similarity between the symptoms of both diseases, the author treated a patient with metaherpetic keratitis with a total tarsorrhaphy and discovered when the adhesions were cut, after four months, that the cornea was perfectly well healed and the patient had almost no leucoma at all. He proposes that this method be tried by others, in order to gain more experience with it. (6 references)

Walter Mayer.

Pietruschla, G. **Familial endothelial corneal dystrophy in combination with glaucoma, vitiligo, and otosclerosis.** Klin. Monatsbl. f. Augenh. 236:794-806, 1960.

The literature on endothelial dystrophy and cornea gutatta is reviewed. A rare case of endothelial dystrophy combined with cataract, vitiligo, otosclerosis, and gastritis is reported. The three children of this 36-year-old man also had corneal changes. (7 figures, 69 references)

Gunter K. von Noorden.

Szeghy, G. **The role of injury in the mechanism of experimental corneal vascularization.** Arch. f. Ophth. 162:215-218, 1960.

Vascularization follows isolated areas of diathermic coagulation of the cornea of the rabbit's eye when the edema extends to the limbus. Checking the development of edema restrains or completely stops vascularization. Absence of continuity of the anterior semipermeable stratum alone—with the development of an edema—does not lead to edema. Thermically coagulated tissue per se does not bring about vascularization. (7 references)

Author's summary.

Van De Velde, J. **Ocular manifestations of a type of superficial punctate viral conjunctivitis.** Ann. d'ocul. 193:710-713, Aug., 1960.

A superficial punctate keratitis is described whose characteristics are a lack of staining with fluorescein but positive staining with mercurobrome. These punctate dots appear around the lacrimal puncta, on the conjunctival surface of the lids, and on the conjunctiva near the limbus in each eye. There is usually a foreign body sensation and lacrimation. This is usually a self-limiting disease which does not respond to antibiotics or to the local application of cortisone. (1 figure, 14 references) David Shoch.

8

UVEA, SYMPATHETIC DISEASE, AQUEOUS

Chatterjee, Sakidas. **Gonio-vessels in normal and abnormal eyes.** Brit. J. Ophth. 44:347-352, June, 1960.

Four types of gonio-vessels were found in normal eyes. They are 1. the circular ciliary vessels which run as a single vessel in the ciliary band, 2. radial iris-root vessels which radiate from the ciliary end of the iris root, are short, and disappear into the iris stroma (they were seen in blue irides only), 3. blood in the canal of Schlemm along the trabecular band, and 4. bunch vessels near the corneoscleral trabecula.

The abnormal vessels consisted of 1. thin radial ciliary vessels found mostly in iridocyclitis, 2. rubeosis iridis, 3. vascular synechiae, and 4. iris root tumors. (1 figure, 1 table, 11 references)

Irwin E. Gaynon.

9

GLAUCOMA AND OCULAR TENSION

Bitran, D. and Arentsen, J. **Scheie's operation for glaucoma.** Arch. chil. de oftal. 16:40-43, Jan.-June, 1959.

The authors present their experience in 30 cases of different types of glaucoma treated by Scheie's method of cauterizing the scleral lip of an incision in order to

produce a fistulizing effect without the danger a subsequent occlusion of the filtering area, as is frequently seen in other types of fistulizing procedures. They believe that it is an easy operation to perform, with good results from a functional standpoint and much better cosmetic results. (3 references) Walter Mayer.

Bitran, D., Barrenechea, S. and Arentsen, J. **Phospholine iodine in the treatment of glaucoma.** Arch. chil. de oftal. 16: 138-142, July-Dec., 1959.

This is a clinical study in which phospholine iodine was used in a series of control eyes and in glaucomatous eyes in which the tension had not been previously kept within safe limits with miotics. The authors feel that this substance controls the tension well and has the advantage that a smaller number of applications is needed; this also prevents diurnal variations of tension. (3 tables, 3 references)

Walter Mayer.

Bitran, D. and Volnitzky, E. **Prevention of glaucoma.** Arch. chil. de oftal. 16: 89-92, Jan.-June, 1959.

The authors systematically studied for glaucoma 1,048 patients who came to their University Clinic during a period of five months. Every patient above 30 years of age had his tension taken with a Schiøtz tonometer and the possibilities of colored halos were explored. Every patient who had a tension between 17 and 24 or complained of colored halos was studied further until glaucoma could either be confirmed or ruled out.

The authors found glaucoma in 11 percent of their patients. They then break down the data on proven cases of glaucomas into tensional values, colored halos, excavated discs and provocative tests. (8 references)

Walter Mayer.

Blancard, P. **Acute glaucoma following general surgical procedures.** Ann. d'ocul. 193:659-666, Aug., 1960.

Twenty-six cases of acute glaucoma following general surgical procedures are described by the author. Most of these cases occurred in the first two days after surgery and most of them in women between the ages of 50 and 70 years. A combination of factors probably causes these acute attacks, but the one common factor is an anatomically narrow angle which predisposes the patient to an acute attack. Unquestionably the emotional and physical shock of surgery plays a part, as well as premedication with atropine or atropine-like drugs. (6 references)

David Choch.

Blatt, N. and Regenbogen, L. **Consensual hypotony in glaucoma surgery.** Klin. Monatsbl. f. Augenh. 136:761-773, 1960.

Results of recent investigations (Thiel and Hollwich) point to the important role of the diencephalon in the pathogenesis of glaucoma. The ocular tension of both eyes was registered tonometrically after filtering surgery had been performed on one eye for chronic simple, chronic congestive, acute, or absolute glaucoma. In most cases a considerable decrease of ocular tension was observed post-operatively in the eye not operated upon. From this observation the author derives the existence of a central neurogenic coordinating mechanism. Changes in vascular permeability in the untreated eye induced by angioneural reflexes elicited from the eye operated upon via the diencephalon, are thought to be the explanation for the phenomenon observed. Hypotony of the eye not operated upon persisted in many cases for several years. Tonometric curves are shown to demonstrate the observations. (10 figures, 9 references)

Gunter K. von Noorden.

Charlin, C. **Rubeosis iridis and glaucoma.** Arch. chil. de oftal. 16:146-149, July-Dec., 1959.

The author presents the clinical find-

ings in a patient with rubeosis iridis and glaucoma which responded well to treatment with pilocarpine and diamox. He feels that this type belongs to the type 3 as described by Favaloro in his classification of rubeosis iridis and glaucoma. (3 figures, 2 references) Walter Mayer.

Gormaz, A. and Eggers, C. **Scheie's operation for glaucoma.** Arch. chil. de oftal. 16:25-31, Jan.-June, 1959.

The author describes his experience with Scheie's operation which consists of a peripheral iridectomy and cauterization of the scleral wound edges in order to produce a fistula which has an advantage over iridencleisis in that there is no iris between the wounds of the lip, the eye looks better when healed and surgery can be repeated in cases of failure. He describes his own technique which differs from the one originally proposed by Scheie in that Tenon's capsule is sutured separately from the conjunctiva in order to prevent a sliding of Tenon's capsule and subsequent obstruction of the filtering area. (4 tables, 8 references)

Walter Mayer.

Lobstein, A., Bronner, A. and Nordmann, J. **The role of ophthalmodynamometry in simple glaucoma.** Ophthalmologica 139:271-275, March-April, 1960.

The difference between the mean retinal arterial blood pressure and the mean intraocular pressure was determined and correlated with the course of the optic nerve disease in 40 cases of chronic simple glaucoma. The period of observation has been too short and the number of cases too small for any conclusions but two important observations have been made. The glaucomatous optic nerve disease is unfavorably ("catastrophically") influenced by phases of arterial hypotension brought on medically or by cardiac decompensation (cfr. Harrington, Am. J. Ophth. 47:177, 1959). Obvious sclerosis

of the retinal vessels renders the prognosis in open-angle glaucoma more unfavorable even in the presence of a large pressure gradient within the eye (the mean arterial pressure being much higher than the intraocular pressure).

Arterial hypotension in cases of open-angle glaucoma calls for antihypotensive treatment. In hypertension with open-angle glaucoma drastic antihypertensive therapy is contraindicated unless the patient's life is in immediate danger (3 figures, 6 references) Peter C. Kronfeld.

Meesmann, A. **Trephine iridencleisis. Report on results obtained.** Klin. Monatsbl. f. Augenh. 136:774-790, 1960.

A surgical procedure is described which combines scleral trephination with iridencleisis; 50 eyes were operated on in this manner. Follow-up examinations up to four and one-half years post-operatively revealed a functioning fistula in 76 percent, normalization of tension in 82 percent, unchanged visual acuity in 80 percent, and no further field loss in 74 percent of the cases. Details of the surgical procedure are given. (4 tables, 2 references) Gunter K. von Noorden.

O'Reilly, G. **Treatment of congenital glaucoma.** Arch. chil. de oftal. 16:44-45, Jan.-June, 1959.

The author briefly reviews the pathogenesis of congenital glaucoma. He feels that goniotomy is the procedure of choice, but there may be many occasions when this procedure cannot be carried out because of the lack of the proper equipment. In such cases he has used Chandler's method for adult glaucoma, using a spatula to separate the ciliary body, with the purpose of separating the membrane which, in the congenital glaucomas, lies in front of the trabeculum. In his series of 13 cases he has obtained good results with normalization of ocular tension.

Walter Mayer.

Sanchez-Salorio, M. and Suarez J. **Inhibitors of carbonic anhydrase and intraocular tension.** Arch. Soc. oftal. hispano-am. 19:925-947, Dec., 1959.

This is a comparative study of the effect of chlorothiazide, hydrochlorothiazide and diamox on the ocular tension. The material comprized ten normal and nine glaucomatous eyes. The action of carbonic anhydrase inhibitors is reviewed, the experimental technique is described in detail, and the data on each eye are reported briefly. The data show that the effect of chlorothiazide and hydrochlorothiazide is inconstant, and that in patients in whom these agents were ineffective diamox produced a significant fall in the intraocular pressure. In the hope of clarifying some of the controversial opinions on the production of aqueous the authors discuss in detail the action of diamox, with special emphasis on the theories of Friedenwald and Green. They point out that diamox reduces the production of aqueous from 40 to 60 percent. This reduction is obtained with comparatively low doses and is not increased by heavy doses of the drug. This suggests that there are at least two sources of aqueous production and that diamox influences one of these. It is also maintained by the authors that diamox raises the tension of the normal as well as of the glaucomatous eye. (5 figures) Ray K. Daily.

Soeteren, T. **Scleral rigidity in normal human eyes.** Acta ophth. 38:303-311, 1960.

The values of the intraocular pressure in emmetropic and slightly ametropic human eyes, as measured with Goldmann's applanation tonometer and Mueller's electronic tonometer, showed good agreement regardless of the pressure level. It is concluded that scleral rigidity does not play an important role for the wide range of normal pressure in these eyes. In normal eyes made hypotonic by compression,

the same difference was found with either tonometer before and after compression. Hence scleral rigidity does not change when the intraocular pressure is artificially decreased. (1 figure, 2 tables, 34 references) John J. Stern.

Tyner, G. S., Lahey, D. D., Elliff, J. F. and Watts, H. E. **Peripheral iridectomy with scleral cauter.** A.M.A. Arch. Ophth. 64:268-274, Aug., 1960.

The technique of Scheie was employed in 42 patients with various types of glaucoma; 34 were controlled without miotics and eight were uncontrolled. In comparison with results of iridencleisis and trephining, this procedure seems to have a higher rate of success, fewer complications, and a wider application. (2 figures, 2 tables, 7 references)

Edward U. Murphy.

Vannas, S. **Hemosiderosis in eyes with secondary glaucoma after delayed intraocular hemorrhages.** Acta ophth. 38:254-267, 1960.

Five eyes were enucleated for secondary glaucoma after central vein occlusion in three or after trauma in two. Hemosiderin was found from three weeks to three months after the hemorrhages; in the posterior part of the eye it occurred in the optic nerve, the retina, the pigment layer, Bruch's membrane and the choroid. Anteriorly it was seen in the epithelial cells of the ciliary body and the walls of scleral and episcleral vessels. These findings suggest different pathways for the outflow of the intraocular fluid in pathologic conditions. (12 figures, 13 references) John J. Stern.

Ytteborg, J. **Aqueous veins during treatment with diamox.** Acta ophth. 38:290-302, 1960.

No significant change in the visible aqueous outflow in the aqueous veins could be observed after diamox medica-

tion by mouth, even when the pressure fell by 50 percent. (1 table, 44 references)

John J. Stern.

10

CRYSTALLINE LENS

Arentsen, J. and Bitran, D. **Comparative study between capsular exfoliation and chronic glaucoma.** Arch. chil. de oftal. 16:74-78, Jan.-June, 1959.

The authors studied 50 cases of capsular exfoliation and compared them with 50 cases of chronic glaucoma. Capsular exfoliation is found in patients over 50 years of age and increases with age; it is much more frequent in the male. In order to make a diagnosis, biomicroscopy must be done with dilated pupils. The glaucomatous symptoms are less manifest in patients with exfoliation than in those with uncomplicated glaucoma. Of the authors' patients with exfoliation 89 percent had glaucoma, 75 percent had cataract, and 68 percent had glaucoma and cataract. Only 5 percent of the patients had exfoliation only, whereas in 95 percent it was associated with either glaucoma or cataract or both. Greater success was achieved by surgical means in patients with exfoliation than in those with pure glaucoma, whereas the reverse was true of medical treatment. (7 references)

Walter Mayer.

Babel, J. **Early post-natal cataract of rapid evolution. Study of four cases, one with histologic examination.** Arch. d'opht. 20:146-153, March, 1960.

Babel describes four cases of progressive early post-natal cataract which he considers to be the complicated type occurring in lenses whose development was abnormal as a result of external influences. These influences may have occurred during the latter part of pregnancy, at birth, or during the first few weeks of life. He considers this type of cataract as one of the group of embryo-

pathic cataracts of unknown etiology. The article is illustrated by five photomicrographs in black and white showing the microscopic anatomy of the cataracts. (5 figures, 6 references) P. Thygeson.

Bitran, D. and Villalobos, Y. **Capsular exfoliation in 100 inmates of an old age home.** Arch. chil. de oftal. 16:79-81, Jan.-June, 1959.

The authors studied 100 elderly persons (50 men and 50 women) without any apparent eye disease. Capsular exfoliation was found in seven percent. Three quarters of the patients without exfoliation had lenticular changes whereas all of the patients with exfoliation had lenticular opacities. The incidence of glaucoma was three percent in the general group as compared with an incidence of 30 percent in those with exfoliation. Walter Mayer.

Bruix, Jorge and Luis Mateos, Jose. **Subconjunctival dislocation of the lens.** Arch. Soc. oftal. hispano-am. 19:967-973, Dec., 1959.

A brief review of the literature is followed by the report of a scleral rupture and a subconjunctival dislocation of the lens in a woman 67 years of age. She fell against a chair and struck the left eye. The subconjunctival dislocation of the lens was discovered after the acute reaction subsided. An intracapsular extraction was performed 17 days after the injury, with a small loss of vitreous. Recovery was uneventful. The final low visual acuity was due to a senile macular degeneration. (6 figures, 9 references)

Ray K. Daily.

Castrén, J. **Trypsin and alpha-chymotrypsin in cataract surgery.** Acta ophth. 38:247-253, 1960.

Among 267 cataract extractions, trypsin was used in 30, and alpha-chymotrypsin in 89 cases; 148 eyes served as controls. The technique was identical in all

cases. Intracapsular extraction was easier and simpler when using enzymes; rupture of the lens capsule was very rare. No effect on posterior synechiae was observed. The corneal wound healed equally well in all groups. Vitreous prolapses occurred in 3.4 percent of the control material, 9 percent of the alpha-chymotrypsin group, and 23.3 percent of the trypsin group. The use of trypsin was therefore discontinued. (3 tables, 19 references)

John J. Stern.

Correa Meyer, R. **Enzymatic zonulolysis of Barraquer.** *Arq. brasil. de oftal.* 23: 7-12, 1960.

The author reports his observations in a series of 179 lens extractions in which alpha-chymotrypsin was used, and compares the results with a control group of 189 extractions done by the Kirby technique. Excluding the cases of congenital cataract, the statistical results favor the use of the enzyme, with a higher percentage of intracapsular extractions and a lower incidence of complications.

In congenital cataract, however, the use of the enzyme seems to be contraindicated because of the high loss of vitreous. In addition, the tumbling of the lens with forceps is not indicated in this technique but should be replaced by grasping the lens at 12 o'clock and sliding it out. There is no discussion of phakoeresis. (5 references)

James W. Brennan.

Fanta, H. and Herold, I. **Late sequelae after enzymatic zonulolysis.** *Klin. Monatsbl. f. Augenh.* 136:506-512, 1960.

One hundred patients were examined at least six months after surgery. Significant complications were not observed. The rather frequent occurrence of delayed wound healing after enzymatic zonulolysis is emphasized and prolonged observation of eyes operated upon in such manner is recommended. (2 tables, 12 references)

Gunter K. von Noorden.

François, J. **XVI Jackson Memorial Lecture. Syndromes with congenital cataract.** *Tr. Am. Acad. Ophth.* 64:433-471, July-Aug., 1960.

Of 217 cases of large congenital cataracts, 45 showed a hereditary factor, 12 showed maternal rubella, six toxoplasmosis, two galactosemia, one syphilis, one influenza, one sulfonamide poisoning.

Specific syndromes are described in order to help delineate congenital cataract into hereditary patterns for easy identification.

Lowe's syndrome consists of renal disease, renal rickets, retardation of physical and mental development, muscular dystrophy, and congenital cataract or glaucoma. Other ocular symptoms are searching nystagmus, enophthalmus, divergent strabismus, Franceschetti's digital-ocular sign, and atrophy of the iris with photomotor areflexia. Other diverse systemic manifestations have been described. All 12 cases occurred in males.

Congenital cataract and oxycephaly have been described in 17 cases. Congenital cataract with other malformations are relatively common, disturbances of fingers and toes are not rare. About 50 cases of cataract associated with congenital stippling of the epiphyses are known. Clinical details of this condition are presented in great profusion.

The Bonnevie-Ullrich syndromes has many associated anomalies, the most characteristic of which is pterygium colli, a broad skin fold from the mastoid to the acromion. Other joint pterygia also occur.

One type of cataract is associated with dyscephaly and bird-face, among other anomalies. Numerous authors have reported this condition in almost innumerable variations.

Congenital cataract can occur with congenital hemolytic icterus. It also occurs in association with oligophrenia, Sjögrens syndrome. This latter is not to be confused with the much rarer Marinesco-

Sjögren syndrome of congenital cataract with spinocerebellar ataxia and mental retardation.

Congenital cataract is not rarely found in mongolism. It is associated with certain skin conditions, including Rothmund's syndrome, Schafer's syndrome, Siemens' syndrome, incontinentia pigmenti, and ichthyosis. (28 figures, 286 references) Harry Horwich.

Gonzalez, F. **Experience with alpha chymotrypsin in cataract surgery.** Arch. chil. de oftal. 16:9-10, Jan.-June, 1959.

The author describes briefly a routine technique for cataract extraction in which alpha chymotrypsin is used. He used this method in 25 cases, in 23 of which extractions were done intracapsularly.

Walter Mayer.

Grom, Edward. **Refraction of the eye before and after cataract extraction.** Arch. Soc. oftal. hispano-am. 20:73-80, Jan., 1960.

The physiologic optics of refraction are reviewed in detail and a formula presented for mathematical calculation of the vertex distance of the correcting lens, based on the postoperative and preoperative refraction. (5 references) Ray K. Daily.

Janes, R. G. and Richards, R. D. **Structural changes of the crystalline lens caused by autolysis.** A.M.A. Arch. Ophth. 64:92-103, July, 1960.

Rats were killed and their eyes removed for study at intervals up to 12 hours after death. Autolytic changes occurred very rapidly and appeared first at the equator. High blood sugar levels at the time of death seemed to intensify these changes. (16 figures, 1 table, 16 references) Edward U. Murphy.

Kachele, G. E. **The embryogenesis of ectopia lentis.** A.M.A. Arch. Ophth. 64: 135-139, July, 1960.

A case of Marfan's disease is presented which showed skin striae. The author postulates that this is not coincidental but is another manifestation of a generalized abiotrophy of the elastic connective tissue of the body. The cardiovascular abnormalities in this syndrome are also due to degeneration of elastic tissue and the same process in the zonule leads to dislocation of the lens. (4 figures, 7 references) Edward U. Murphy.

Keerl, G. **The cataract in idiopathic hypoparathyroidism.** Ophthalmologica 139: 363-373, May, 1960.

Hypoparathyroidism is considered as idiopathic if its manifestations are not preceded by a surgical procedure in the region of the neck. Such idiopathic hypoparathyroidism has been diagnosed in children, adolescents and in adults. The idea underlying the present study is that the lens opacities which are present in more than 50 percent of all cases of hypoparathyroidism might serve to define the time of its onset. Particularly a prenatal onset of the endocrine disturbance should cause lens opacities different from those developing during the second or third decade of life. There also was the possibility of the lens opacities facilitating the distinction between true and so-called pseudo-hypoparathyroidism, the latter condition being characterized principally by lack of the typical response to a single dose of para-hormone. A typical case of this pseudo-hypoparathyroidism is reported. Other reports in the largely non-ophthalmologic literature are unfortunately not detailed enough to allow distinction between lens opacities of prenatal or postnatal onset. (30 references)

Peter C. Kronfeld.

Kittel, V. **Acquired lens colobomas.** Klin. Monatsbl. f. Augenh. 136:540-544, 1960.

Three cases are reported. Retardation

of growth of the lens was the result of defects in the zonula after surgery for glaucoma at an early age. (5 figures, 5 references) Gunter K. von Noorden.

Norskov, K. **Expulsive hemorrhage caused by succinylcholine.** *Acta ophth.* 38:285-289, 1960.

A 70-year-old patient with diabetes had his cataract extracted under light general anesthesia, the use of alphachymotrypsin and one McLean suture. After the operation was concluded, the patient reacted with coughing to the ventilating tube and 50 mg. of succinylcholine were given intravenously to stop it. This was immediately followed by an expulsive hemorrhage which led to evisceration. (18 references) John J. Stern.

Ogg, A. J. **Photography of lens opacities by trans-scleral illumination.** *Brit. J. Ophth.* 44:374-377, June, 1960.

A method whereby lens opacities were photographed by the light reflected from the retina in transpupillary transillumination is described. A transluminator and a reflex camera are used. The lens opacity is seen as a white area against a dark background. (3 figures, 3 references) Irwin E. Gaynon.

Olivares, M. **Adjunct to stripping of the zonula.** *Arch. chil. de oftal.* 16:128-130, July-Dec., 1959.

The author practices the stripping of the zonula after total iridectomy and wide midriasis in a large number of his cataract extractions. He has found that in spite of the stripping, there sometimes is great resistance to breaking the rest of the zonular fibers and he doubts seriously that external pressure over the limbus area breaks these fibers without greatly disturbing the vitreous. He therefore uses a traction suture as described by Sullivan, which is inserted in the sclera at the six o'clock position about three millimeters

from the limbus. Traction on this suture will break the inferior zonular fibers more effectively than pressure and much more safely. (2 references) Walter Mayer.

Paufique, L. and Royer, J. **Unexpected post-operative complications after cataract extractions due to the anterior vitreous.** *Ann. d'ocul.* 193:545-560, July, 1960.

The authors discuss two complications that occur occasionally after cataract surgery. One is an adhesion of the anterior vitreous to the posterior surface of the cornea, and the second a degeneration of the intact anterior vitreous face. Most of these complications occur after routine intracapsular extraction. The authors feel that the adherence of the vitreous to the corneal endothelium is a result of two factors: 1. a herniation forward of the vitreous through a round pupil and 2. an injury of the endothelium at the time of surgery either by instruments or by the cataract itself. The second complication, that of degeneration of the vitreous face after cataract extraction, seems to occur more commonly with the use of chymotrypsin.

Treatment of these two conditions is outlined as follows: An incision is made in the cornea at 12 o'clock and a complete iridectomy is performed. The vitreous is then allowed to prolapse, or is even drawn out with forceps and cut off flush with the wound. The pre-placed suture is then drawn up in such a fashion as to incarcerate the vitreous face in the wound. A large bubble of air is then inserted into the anterior chamber via a pre-placed track made at 6 o'clock. In most cases the corneal dystrophy will gradually clear. (8 figures, 7 references) David Shoch.

Redslob, E. **Zonulolysis of J. Barraquer.** *Ann. d'ocul.* 193:598-605, July, 1960.

The author reviews the literature on alpha-chymotrypsin and comes to the conclusion that the use of the enzyme is a

great step forward in cataract surgery. He emphasizes the risks involved in the use of chymotrypsin in the infant and child and lists the various complications reported in the literature. Details of technique are briefly mentioned. (35 references) David Shoch.

Rohrschneider, W. and Friedrich, H. **Late sequelae after cataract surgery with zonulolysis.** Klin. Monatsbl. f. Augenh. 136:499-506, 1960.

A review of publications regarding complications following enzymatic zonulolysis is given; 126 eyes were re-examined 9 to 18 months after surgical zonulolysis. Glaucoma had occurred in only one of the eyes examined. Conditions resulting from delayed wound healing were observed relatively frequently; however, interference with ocular functions was not present in any of these cases. The vitreous protruded into the anterior chamber in 20 percent of the cases. (5 tables, 26 references) Gunter K. von Noorden.

Shimkhovich, I. S. and Shilyaev, V. G. **Bilateral cataract produced by repeated short exposures to a high frequency high density electromagnetic field.** Vestnik oftal. 4:12-16, July-Aug., 1959.

A young man, aged 22 years, developed bilateral cataract as a result of exposure to high frequency electromagnetic waves of the order of 10 cm. The opacities resembled cotton wool in appearance and were hemispherical in shape. They were separated by transparent layers from the anterior and posterior capsule and from the nucleus of the lens. The development of the cataract was rapid. (11 references) Victor Goodside.

Silvan, F. **New instruments for use in cataract extraction.** Brit. J. Ophth. 44:315-318, May, 1960.

Two new instruments for cataract surgery are briefly described. The erisiphake

is modified in that the suction is controlled by a pedal. The cataract knife is inverted in that the blade itself is on a pivot facing the handle which enables the surgeon to use his right hand more easily on either eye. (5 figures, 14 references)

Morris Kaplan.

Townes, C. D. **Unfavorable effects of alpha-chymotrypsin in cataract surgery.** A.M.A. Arch. Ophth. 64:108-113, July, 1960.

The course and results of 134 cataract extractions, half with use of the enzyme and half without, were analyzed. The author concludes that this preparation has a retarding effect on wound healing, that it need not be used in patients over 70 years of age, that it should not be used in children, and that at least five corneo-scleral sutures be inserted. (7 tables, 4 references) Edward U. Murphy.

Urrets-Zavalía, A. **Deturgescence of the vitreous, pharmacologically induced prior to cataract surgery.** Klin. Monatsbl. f. Augenh. 136:753-761, 1960.

Vitreous pressure is a dangerous complication during cataract surgery. To prevent it the author treats his patients with diamox (15 to 20 mg./kg body weight per day) 48 hours before surgery. Vitreal hypotony resulted and vitreal loss did not occur in 87 eyes prepared for surgery in this manner. (12 figures, 14 references)

Gunter K. von Noorden.

de Vincentiis, M. **The pathogenesis of cataracta complicata: an experimental study.** Ophthalmologica 139:374-382, May, 1960.

Cataracta complicata comparable to that of man was produced in rabbits as a sequel to experimental anaphylactic uveitis or to degeneration of the retina due to mono-iodoacetate poisoning. The effects of these two procedures upon the chemistry of the proteins of lens and vit-

reous were studied by electrophoresis. The electrophoretic pattern of the soluble proteins of the posterior lens cortex showed significant deviations from the normal during early stages of the complicated cataract. These changes occurred characteristically in those portions of the lens that were closest to the diseased vitreous. (5 figures, 28 references)

Peter C. Kronfeld.

Welsh, R. C. **Contact lenses for aphakics.** *A.M.A. Arch. Ophth.* 64:251-253, Aug., 1960.

The details and specifications of such a lens are given and its problems discussed. An aphakic patient can be "overplussed" by 0.5 or 1.0D. and will have good distance vision and fair near vision. Ordinary bifocal spectacles can then be worn when better vision is needed at either distance. (1 figure)

Edward U. Murphy.

11

RETINA AND VITREOUS

Arques, E. **A case of bilateral occlusion of the central retinal artery and retinal detachment.** *Arch. Soc. oftal. hispano-am.* 20:323-326, April, 1960.

This is a report of the complicated case of an 18-year-old pregnant girl, who presented herself with a typical picture of embolus of the central retinal artery in the left eye, and less typical signs of the same process in the right eye. The management was complicated because of lack of cooperation on the part of the patient and her parents. The patient insisted that she was seeing well in spite of objective evidence to the contrary. Under the care of another ophthalmologist she subsequently developed a bilateral retinal detachment. The peculiar attitude of the patient was finally clarified when it was discovered that the young man responsible for the pregnancy was refusing to marry the girl until he was assured that she had recovered from her visual dis-

turbance. This accounted for the unwillingness of the patient to take the prescribed medication and to admit visual inadequacy. In view of the history and subsequent course of the disease the author attributes the disturbance to an initial angiospasm caused by an abortifacient. It is believed that the intense and persistent angiospasm in the fundus assumed a picture typical of arterial obstruction. In retinal angiospasm vision may be completely abolished and the ophthalmoscopic appearance may be identical with that of embolism of the central retinal artery. The improvement in visual acuity supports the diagnosis of angiospasm.

Ray K. Daily.

Badtke, G. **Genetico-physiological connections between congenital falciform retinal detachment and pathological developmental processes of the retina in the area of the fetal orbital fissure, with special regard to typical colobomas of the fundus.** *Klin. Monatsbl. f. Augenh.* 136:806-815, 1960.

A 14-year-old boy was seen who had a falciform detachment of the retina and a persistent hyaloid artery, combined with coloboma of the disc and choroid. It is pointed out that the primary developmental cause for falciform detachment should be looked for in defects of tissues forming the ectodermal optic cup, rather than in mechanical action of the persistent hyaloid vessel. The latter may play a secondary role in the development of the final clinical picture of falciform detachment. The different views on this subject are extensively discussed. (1 figure, 31 references)

Gunter K. von Noorden.

Bangerter, A. **Therapy of macular holes.** *Klin. Monatsbl. f. Augenh.* 136:593-598, 1960.

The author disagrees with Meyer-Schwickerath who claims that light coagulation is the therapy of choice in macular

holes with flat detachments. He prefers retrobulbar implantation of placenta or amnion. The author objects also to the use of light coagulation for the treatment of macular holes without detachment and as a therapeutic trial in cases where it is difficult to differentiate between a macular hole and a cyst. (8 references)

Gunter K. von Noorden.

Castroviejo, R. **Retinal detachment surgery: scleral shortening by outfolding with titanium clips.** *Tr. Am. Acad. Ophth.* 64:472-485, July-Aug., 1960.

The current technique for shortening the sclera by folding outwards is described. The subretinal fluid is drained first, then the sclera is outfolded with forceps and held shortened by 4-mm. titanium clips. These may be placed in single or multiple rows, in equatorial or meridional directions or both, and in variable numbers.

Electrocoagulations are used about the folding as in other methods. Vitreous or air may be injected if the retina remains elevated after the scleral outfolding. Sixty-seven operations have been done in 56 eyes; in 30 of them the retina remained attached and in 26 there was failure, but the prognosis in those was very poor. The titanium clips were well tolerated. (13 figures, 3 references) Harry Horwich.

Charlin, C. and Quiroz, R. **Retinoblastoma treated according to Reese's technique.** *Arch. chil. de oftal.* 16:66-73, Jan.-June, 1959.

The authors discuss the general symptomatology of retinoblastomas and briefly describe the different types found. As to treatment, they feel that if only one eye is involved it should be enucleated with as much of the optic nerve as possible. In case of bilateral tumor the more involved eye should be enucleated and the other eye should be treated with radiotherapy and TEM, according to the schedule

worked out by Reese. This method of treatment should be used when the second eye has only about one-third of its retina invaded; whenever the growth is more extensive, enucleation of this second eye should also be done to save the child's life. The authors discuss briefly three patients so treated. (4 references)

Walter Mayer.

Choremis, C., Joannides, J. and Kyriakides. **Severe ophthalmologic complications following favism.** *Brit. J. Ophth.* 44:353-356, June, 1960.

Two cases of severe hemolytic anemia following the ingestion of broad beans in children are reported. The first patient had wide-spread ecchymosis, no light reflex, discs were blurred, distended veins were tortuous, and the posterior pole had many preretinal and retinal hemorrhages. In the second case there was slight papilledema, narrowing of the retinal arteries, small hemorrhages about the disc, and sudden loss of vision seven days after the hemolytic onset. (9 references)

Irwin E. Gaynon.

François, J. and Verriest, G. **A new observation on atypical hemeralopia.** *Ann. d'ocul.* 193:493-500, June, 1960.

The authors report a second case of poor dark vision, verified by electroretinography. As in their first case there was a history of hepatitis but no change in vitamin A or carotenoid levels in the blood. They feel, therefore, that this is not a vitamin A deficiency syndrome but a disease of the visual pigments perhaps due to the old hepatitis. (2 figures, 1 reference)

David Shoch:

François, J., Verriest, G., De Rouck, A. and Rabaey, M. **Comparative study of the retinal histology and the electroretinogram in batrachians and reptiles.** *Ann. d'ocul.* 193:667-707, Aug., 1960.

This is the second in a series of three

articles on the retinal structure and physiology of batrachians and reptiles. This second article is devoted to personal investigations of the authors and is divided into two sections. The first deals with the retinal histology of the experimental animals and the second with the electroretinogram. Forty different specimens were examined. Among the amphibia were salamanders, toads and frogs. Among the reptiles were crocodiles, chameleons and colubrid snakes. A histologic picture of the retina in each of these 40 specimens is given.

The electroretinogram was made on the eyes of these animals immediately after enucleation. However, the eyes were not incised. Details of the tracings are given for most of the specimens. (43 figures)

David Shoch.

Gartner, J. **Hereditary equatorial degenerations in nonmyopes. Solitary forms and oro-parallel bands.** *Klin. Monatsbl. f. Augenh.* 136:523-539, 1960.

Equatorial degeneration of the retina occurred in one family. Two types of degeneration are reported which have not been described before: a band or galaxy-like degeneration parallel to the ora, and a combination of this form with cystoid retinal holes. A hereditary developmental disturbance or abiotrophy is assumed to be the cause of this condition. Other types of equatorial degenerations are reviewed and discussed. (4 figures, 27 references)

Gunter K. von Noorden.

Gates, R. F. and Richards, R. D. **Macroglobulinemia and unusual vascular changes.** *A.M.A. Arch. Ophth.* 64:77-80, July, 1960.

In addition to the previously described venous changes in the fundus, the cases reported here showed aneurysmal dilations of the larger arterial branches and microaneurysms in the periphery.

Edward U. Murphy.

Graham, P. A. and Sevens, P. R. **Surgical results in acute glaucoma.** *Brit. J. Ophth.* 44:357-362, June, 1960.

A review of 156 consecutive cases initially diagnosed as acute-angle glaucoma is given. Comparison is made between 1. intensive eserine therapy followed by iridectomy. 2. an intermediate group where the patient was brought under control with miotics and diamox, and 3. the group wherein the patient has undergone intensive miotic and diamox therapy, followed by minimum miotic therapy and iridencleisis or trephining. Causes of failure consisted of hyphema followed by raised ocular tension, raised tension, uveitis, cupping and loss of field. The results were much better when surgery had been performed after the eye had recovered from the acute episode and a more thorough investigation was possible. (4 tables, 6 references)

Irwin E. Gaynon.

Gratmore, Clive. **Metabolism of the developing retina. III Respiration in the developing normal rat retina and the effect of an inherited degeneration of the retinal neuro-epithelium.** *Brit. J. Ophth.* 44:363-369, June, 1960.

The behavior of the retina of the rat in bicarbonate buffer suggests that the respiratory changes during development closely parallel those of glycolysis. Respiratory capacity is doubled during the second and third weeks of life. The fall in respiratory activity in the retina with hereditary degeneration of the retina of the rat follows the same pattern as previously reported for glycolysis. (1 figure, 1 table, 21 references)

Irwin E. Gaynon.

Larsen, H. W. **Diabetic retinopathy. An ophthalmoscopic study with a discussion of the morphologic changes and the pathogenic factors in this disease.** *Acta ophth. Suppl.* 60, 1960. (89 pages)

The history and literature of diabetic retinopathy are reviewed in the first two

chapters. The third chapter describes the development and course of the condition. It develops over the course of several years, starting with dilatation of the veins, microaneurysms or punctate hemorrhages; their number increases, deep hemorrhages and exudates appear, enlarge and tend to become confluent. In most cases the retinopathy stops here; in some it proceeds to a proliferative stage, with neovascularization, preretinal and vitreous hemorrhages, degeneration of the hyaloid membrane, vitreous detachment, fibrous tissue formation, retinal detachment, and sometimes rubeosis iridis and hemorrhagic glaucoma. In older diabetics it is characteristic that exudates often appear early. In some juvenile diabetics, retinopathy sometimes proceeds from venous dilatation directly to a proliferative stage. The next chapter describes in detail the inter-relationship, mode of development, and ophthalmoscopic and histologic appearance of the fundus lesions. In chapter V the relationships between diabetic retinopathy and diabetic nephropathy, cardiovascular changes and neuropathy are reviewed. All these changes are mainly due to diabetic angiopathy in the small arteries, arterioles, and capillaries and are characterized by degeneration of the vessel wall and hyalinization of the basement membrane. Chapter VI discusses possible pathogenic relationships between changes in the serum lipids, lipoproteins and mucopolysaccharides, pituitary-adrenocortical hyperfunction and hypercoagulation, and the development of diabetic retinopathy. No single factor can be responsible for diabetic angiopathy. In Chapter VII the possible role of local factors is discussed; vascular dysfunction and variations in the intraocular pressure may be responsible for the dilatation and varying fullness of the veins in the early stages. They may also contribute to the production of microaneurysms and hemorrhages. Proliferative diabetic retinop-

athy is possibly a reaction to a state of chronic subnutrition. Most therapeutic attempts have so far failed. Careful treatment and good control of the diabetes are the requirements for good results. (222 references) John J. Stern.

Lijo Pavia, J. **Diabetic retinopathy treated successfully with prednisolone acetate by retrobulbar injection.** Rev. oto-neuro-oftal. Sudam. 34:29-33, June-Sept., 1959.

The author describes briefly the pathogenesis and grades of diabetic retinopathy and then describes in detail five cases which he has treated by retrobulbar injection of 12 mg. of prednisolone acetate, at weekly intervals. This dose is too small to give any unfavorable systemic reactions. The patients have improved markedly, not only ophthalmoscopically but also in objective visual acuity. (2 figures, 14 references) Walter Mayer.

Lijo Pavia, J. and Campagnoli, M. **Treatment of diabetic retinopathy with retrobulbar prednisolone acetate.** Rev. oto-neuro-oftal. Sudam. 34:34-35, June-Sept., 1959.

This paper is essentially the same as another paper by the same principal author (L P) published in this issue. Here he describes extensively the general physical and ophthalmologic findings in a diabetic patient whose retinopathy has been successfully treated with retrobulbar injections of prednisone acetate. (12 references) Walter Mayer.

Molnar, L. **The applicability of electroretinography in surgery for retinal therapy.** Arch. f. Ophth. 162:124-131, 1960.

Molnar discusses the significance of the b-wave of the electroretinogram in surgical therapy. The height of this wave supports a diagnosis in the presence of vitreous opacities, it helps in prognosis, and aids in evaluating the success of surgery

by comparison of the height of the wave before and after surgery. (5 tables, 10 references)

F. H. Haessler.

Mourgues, G. **Histologic findings in an eye with retinal detachment operated upon after Custodis.** *Klin. Monatsbl. f. Augenh.* 136:598-603, 1960.

The procedure consisted of electrocoagulation combined with scleral implant. The patient died three weeks after surgery. The tissues adjacent to the plastic implant showed marked inflammatory connective tissue reactions. Apart from the mechanical action of the implant, it is felt that the irritative effect of the plastic material used for scleral implants is of therapeutic value in detachments. (5 figures, 4 references)

Gunter K. von Noorden.

Orts Llorca, F. and Genis Galvez J. **Congenital retinal folds.** *Arch. Soc. oftal. hispano-am.* 20:91-108, Feb., 1960.

The literature on the subject is reviewed in detail and reference made to the authors' experimental work with chickens. This investigation comprises the anatomic and histologic study of 36 human embryos of which 21 were from 20 to 25 mm. and 14 from 36 to 78.5 mm. in size. The study shows that in embryos 20 to 25 mm. in size there are normally present flat folds, produced by a disparity in the growth of the neural end of the pigmentary portions of the retina. These folds are in contact with the primary perihyaloid vitreous. Later the retina flattens out and the folds disappear. In some cases they persist during the fetal period. In 11 fetuses of the 14 between 36 and 78.5 mm. in length, the sections showed that the retina was concave and smooth, with no vestige of folds or irregularities. In three fetuses, however, retinal folds were observed. In a fetus of 46 mm. there was a definite fold in the periphery of the inferior retinal quadrant. In a fetus of 50 mm.

there were several irregular folds in the temporal quadrant of the retina of the right side with projections which gave them the appearance of rosettes; and finally in a fetus 74 mm. in length there was in the inferior temporal quadrant of both eyes a fold, which started temporally at some distance from the disc, traversed the vitreous in the form of a cord, and was attached to the peripheral portion of the retina. In all three fetuses the folds consisted of neural epithelium, of which the pigmentary portion was uninvolved and the differentiation of the retina in the folds was defective in comparison with the rest of the retina. The authors conclude that their data confirm Mann's theory of the pathogenesis of these folds. This study indicates that the folds in the small embryos are transitory formations in the course of normal ontogenesis, and that as the optic cup invaginates and the retina separates from the primary vitreous by the interposition of the secondary vitreous the folds disappear and the retina assumes a smooth and concave form. It is logical that the progressive development of these folds would result in a congenital malformation. (9 figures, 2 tables, 38 references)

Ray K. Daily.

Perez Martinez, Luis F. **Prophylaxis of retinal detachment in aphakics.** *Arch. Soc. oftal. hispano-am.* 20:57-65, Jan., 1960.

The literature on the subject is reviewed and a case is reported in which the second eye of a patient, who lost the fellow eye from retinal detachment following a cataract operation, was operated upon with a satisfactory result. The left eye was lost from a retinal detachment one month after an uneventful cataract extraction. The progressive lenticular opacity of the other eye demanded action. The procedure which the author followed comprised diathermy coagulation at the equator of the superior ocular semicircumference, followed two months later by

the same procedure on the inferior semi-circumference, and four months later by an intracapsular cataract extraction. Over an observation period of ten months this eye developed no complications. (2 figures, 7 references) Ray K. Daily.

Pietruschka, G. **Differential diagnosis between Grönblad-Strandberg syndrome and Siegrist streaks.** Klin. Monatsbl. f. Augenh. 136:635-649, 1960.

The literature on Grönblad-Strandberg syndrome is reviewed. Since angioid streaks may occur in considerable morphologic variations, it is of importance to be able to differentiate between these lesions and Siegrist streaks. While the former are part of a syndrome involving elastic tissue, the etiology of the latter is still obscure. On the basis of his material, the author describes the ophthalmoscopic differences in these lesions. (8 figures, 92 references) Gunter K. von Noorden.

Rieger, H. **The etiology of retinitis exudativa externa centralis.** Arch. f. Ophth. 162:178-192, 1960.

The author again describes this retinal lesion which he had first described in 1937 and 1939 and he briefly summarizes the literature on the relationship of this lesion to toxoplasmosis in the adult. He then reports 50 unselected cases observed by him. His analysis of the data leads him to conclude that this retinal lesion is a readily recognizable sign of acquired adult toxoplasmosis. (3 tables, 64 references) F. H. Haessler.

Singh, S. and Dass, R. **The central artery of the retina. A study of its distribution and anastomoses.** Brit. J. Ophth. 44: 280-299, May, 1960.

There has been great divergence of opinion regarding the central artery of the retina and its branches and its anastomoses; this study goes into detail about this artery, its communications and its

distribution. The author studied 106 human orbits and 100 of the arteries were injected with liquid neoprene latex. In the other six specimens the part of the optic nerve containing the artery was sectioned serially. In 64 specimens branches were found arising from this artery and these branches could also be injected and studied; there was no uniform pattern as to where these branches arose and to what caliber they grew. They arose from all along the course of the central artery except at the lamina cribrosa.

Numerous anastomoses of these branches were found; they were particularly numerous around the pial section of the artery. These communications were with the pial branches of the circle of Zinn and with collateral branches of the ophthalmic artery and were found to be quite numerous.

There has been some doubt as to the presence of branches of the central artery of the retina supplying the optic nerve itself but in this series such branches were definitely found. They supplied the nerve from the eyeball to the optic foramen and also the dural sheath of the nerve. (23 figures, 33 references) Morris Kaplan.

Tiburtius, H. **Retinal vein occlusion.** Klin. Monatsbl. f. Augenh. 136:604-617, 1960.

The causes of the increased occurrence of retinal vein occlusion are discussed. Vascular sclerosis, allergic-hyperergic intima proliferation, tuberculosis, lues, and trauma are etiologic factors to be considered. The treatment with anticoagulants is reviewed. The author reviews his material which consists of 104 patients with venous occlusions. Among them were 34 branch occlusions and 70 central vein occlusions; 37 patients received treatment with anticoagulants, 67 patients were treated with hemostatic drugs or irradiation. The results revealed that although glaucoma occurred less often in the first

group, general improvement hardly exceeded the results achieved without anticoagulants. In fact, the occurrence of secondary retinal hemorrhages after anticoagulant therapy may lead to pronounced impairment. On account of his observations, the author would at present not recommend the use of anticoagulants in retinal vein occlusions. (2 tables, 63 references) Gunter K. von Noorden.

Vannas, S. **Electroretinographic observations in central vein occlusions.** *Acta ophth.* 38:312-321, 1960.

Thirty-two eyes with central vein occlusion, 16 of them in the late stages with simple glaucoma, were examined. The ERG of the eyes without glaucoma was generally normal and vision was good; only two with exceptionally profuse hemorrhages showed a negative ERG. In the eyes with occlusions and glaucoma the ERG was usually negative, sometimes completely extinguished. Only in two cases was it normal and vision was normal in one of these. In cases of occlusion with glaucoma a subnormal ERG was possible for the fellow eye, in those without glaucoma it was normal. Electroretinography is an aid in the prognosis for central vein occlusion. (2 tables, 3 figures, 14 references) John J. Stern.

Weekley, R. D., Potts, A. M., Reboton, J. and May, R. H. **Pigmentary retinopathy in patients receiving high doses of a new phenothiazine.** *A.M.A. Arch. Ophth.* 64:65-76, July, 1960.

Thioridazine is a new drug used in the treatment of psychiatric patients. Four cases of pigmentary degeneration of the retina following therapy with this drug are presented. Visual acuity was permanently lowered and none of the patients showed improvement after withdrawal of the medicine. (7 figures, 39 references) Edward U. Murphy.

Yui-Chzhin, I. **The change of the interstitial substance of the retina by radiation energy.** *Vestnik oftal.* 4:5-12, July-Aug., 1959.

Changes in the retina were produced experimentally in rats both by X-ray irradiation of the whole body as well as of the head and eyes. Clouding of the retina developed and was more marked the higher the dose of radiation. Maximum changes followed irradiation of the whole body. Improvement in the general condition of the animal was associated with restoration of transparency of the retina. Vasodilation and vasoconstriction of the retinal vessels were also noted. On histologic examination the interstitial substance of the retina was found to be swollen. (6 figures, 12 references)

Victor Goodside.

12

OPTIC NERVE AND CHIASM

Bonel, L. and Salles, P. **Isolated primary lesions of the optic nerve in the Congolese, around Brazzaville.** *Ann. d'ocul.* 193:465-484, June, 1960.

Twenty-five cases of primary optic atrophy are reported in negroes living in the Congo near Brazzaville. Detailed examination of the central nervous system and the blood failed to reveal a specific cause for these cases. Malnutrition may be implicated and tobacco may be a factor. Alcoholism is definitely not a factor. There were five instances of filariasis but this may be a coincidental rather than an etiologic finding. At least three patients had classical signs of chiasmal arachnoiditis and improved with steroid therapy. (8 references) David Shoch.

Dex Prez, R. M. and Jordahl, C. W. **Problem of optic atrophy complicating tuberculous meningitis.** *Ann. Int. Med.* 52:1118-1122, May, 1960.

The use of steroids in the presence of bacterial infections, often catastrophic

initially, is becoming more and more popular, with the knowledge of the benefits often to be obtained, providing the infecting agent is adequately covered by antibiotics or chemotherapy. It is suggested in this article that such may be the case with one of the most disastrous complications of tuberculous meningitis. Two cases of this disease are presented, both of which demonstrated complete blindness on recovery from an initial coma. Both patients received adequate anti-tuberculosis therapy from the start. One did not receive steroids until seven weeks after the onset; no recovery of vision took place. The other was treated with steroids within 24 hours of the onset; sight had partially returned within two weeks and was normal within three. The writers believe that the apparent effectiveness of steroids may be due to a hampering of the development of hyperplastic inflammatory tissue at the chiasm.

Lawrence T. Post.

Mikuni, M. Ishii, K. and Makabe, R. **Diameter of the optic disc in Japanese people.** *Klin. Monatsbl. f. Augenh.* 136: 544-557, 1960.

The diameter of the optic disc was measured anatomically in 50 male and female cadaver eyes. The average diameter was found to be 1.618 mm. horizontally and 1.796 mm. vertically. The diameter of the male eyes was slightly longer than those of the female eyes. Size or age differences could not be established. For comparative purposes histologic sections were made in seven eyes after formalin fixation and colloidin embedding of the specimen. Measurements of the disc revealed an average shrinkage of 9.337 percent. (9 tables, 12 references)

Gunter K. von Noorden.

Morales, M. **Optic neuritis during lactation.** *Arch. chil. de oftal.* 16:143-145, July-Dec., 1959.

The author describes the experience of two patients who developed optic neuritis during lactation, a rare complication which may occur during the seventh to tenth week after delivery. Lactation must be interrupted and the patient be given steroids. The neuritis can be a papillitis or the retrobulbar type and prognosis must be guarded as in any other optic neuritis. The exact pathogenesis of this neuritis is unknown. (1 figure, 5 references)

Walter Mayer.

Spitsin-Yakubovskii, K. G. **A rare case of bilateral vascular fossa on the papilla of the optic nerve.** *Vestnik oftal.* 4:45-46, July-Aug., 1959.

A round depression near the temporal margin of each disc, $\frac{1}{2}$ disc-diameter in size, was found in a 23-year-old female with bilateral macular degeneration. Several small arteries and veins were seen running from under the margins of the depression towards the macula. (1 photograph, 2 references)

Victor Goodside.

Vena Rodriguez, Antonio. **Differential diagnosis of edema of the optic disc and papillitis, with the biomicroscope.** *Arch. Soc. oftal. hispano-am.* 20:66-72, Jan., 1960.

The difficulties of the differential diagnosis between edema of the optic disc and papillitis are discussed. Reference is made to the work of Wolter, Busacca and Goldman, and the differential points, which identify biomicroscopically edema of the papilla and papillitis are listed. It is pointed out that advanced cases of edema of the optic disc may develop inflammatory signs which complicate the diagnosis. (1 figure, 13 references)

Ray K. Daily.

Victor, M., Mancall, S. L. and Dreyfus, P. M. **Deficiency amblyopia in the alcoholic patient.** *A.M.A. Arch. Opth.* 64:1-33, July, 1960.

Fourteen alcoholic patients were stud-

ied and all showed the picture of impaired central vision, central and centrocecal scotomata, intact peripheral fields and minimal fundus changes. In the patient examined pathologically there was degeneration in both optic nerves, chiasm and tracts, limited to the pathway of the papillomacular bundle. It is nutritional deficiency and not the toxic effect of alcohol or tobacco which causes this ocular disorder. (29 figures, 1 table, 43 references)

Edward U. Murphy.

13

NEURO-OPHTHALMOLOGY

Braun-Vallon, S. and Bessman, N. **Familial dysfunction of the autonomic nervous system. (Riley-Day syndrome)** *Ann. d'ocul.* 193:561-569, July, 1960.

The typical Riley-Day syndrome has many manifestations all of which indicate an autonomic dysfunction. It is generally familial in nature and occurs primarily in Jews. The symptoms include deficient lacrimal secretions, excessive sweating, emotional instability, indifference to pain, frequent pulmonary infections, unexplained fever, and in about one-third of the cases corneal ulcerations.

The authors report three cases of which one, in a child, two years of age, showed a complete syndrome and two further cases in a sister and brother showed incomplete forms of the syndrome. The last two children were not Jewish, and it is reported that in these children the syndrome usually is incomplete. In all cases there was a diminution of tearing. (30 references)

David Shoch.

Hoyt, W. F. **Vascular lesions of the visual cortex with brain herniation through the tentorial incisura.** *A.M.A. Arch. Ophth.* 64:44-57, July, 1960.

Increased supratentorial pressure may produce herniation of the brain through the tentorial incisura and compress the

posterior cerebral arteries. A rapidly developing homonymous hemianopsia is produced and is caused secondarily rather than by the primary lesion. (8 figures, 21 references)

Edward U. Murphy.

Marin-Amat, M. **The association of homonymous hemianopsia and recurrent vitreous hemorrhages.** *Arch. Soc. oftal. hispano-am.* 20:297-317, April, 1960.

The author reports the case of a 37-year-old man who fell from a height of four meters, was badly shocked, remained unconscious for 11 days, and four days later suddenly lost vision in both eyes. He was found to have retinal hemorrhages. X-ray study of the cranium was negative, and the Mantoux reaction was strongly positive. Blood studies were found to have normal values and in spite of treatment with rest, coagulants and streptomycin the retinal hemorrhages kept recurring for a period of two years. When exploration of the visual fields became possible the patient was found to have a right bilateral homonymous hemianopsia. At the same time a typical process of retinitis proliferans made its appearance; this caused no visual disturbance in the right eye, but produced a detachment of the retina in the left eye, which was reattached surgically. The hemorrhages became gradually less intense and central visual acuity was restored to normal in the right eye and to 20/40 in the left. The etiology of the hemianopsia is discussed and the literature on the subject reviewed in detail. Because of the absence of other symptoms caused by intracranial hemorrhage it is concluded that the hemorrhage causing the hemianopsia in this case was located in the left optic radiation. Two other cases of homonymous hemianopsia are reported, one caused by a hemorrhage in the left internal capsule, and one by a glioblastoma of the right occipital region. In both of these cases the hemianopsia

was accompanied by other symptoms of intracranial disturbance. The recurrent retinal hemorrhages are attributed to the stimulation of the vegetative centers by microhemorrhages in the hypothalamus. (11 figures) Ray K. Daily.

Wendland, J. P. and Nerenberg, Sidney. **Visual field studies after temporal lobectomy for epilepsy.** A.M.A. Arch. Ophth. 64:195-200, Aug., 1960.

The field defects in 24 patients were remarkably congruous and indicate that fibers from corresponding retinal points lie close together in the anterior portion of the optic radiations. The authors conclude that the controversial Meyer's loop does exist. (7 figures, 1 table, 13 references) Edward U. Murphy.

14

EYEBALL, ORBIT, SINUSES

Aron, J. J. **Ocular toxoplasmosis.** Ann. d'ocul. 193:521-528, June, 1960.

This article is a general review on toxoplasmosis. The author divides toxoplasmosis into three categories: congenital, acquired, and relapses of the congenital form. He describes each type and in the second section of this article gives the systemic findings. In the third section he reviews the diagnostic tests available for toxoplasmosis. He feels that the most sensitive test is inoculation of an experimental animal such as the guinea pig, with cerebral spinal fluid or biopsy material. Since this is rarely possible, one must rely more often on the "dye-test" or complement fixation test. He feels that these two are not nearly as specific as the first mentioned. (17 references)

David Shoch.

Cavalheiro Willmersdord, J. and Renata Attadia, E. **Intraorbital epidermoid cyst.** Arq. brasil. de oftal. 23:19-22, 1960.

This is a case report of an 18-year-old

girl who had a marked exophthalmos with limitation of movement of the globe for eight years. After confirming the diagnosis of a space-occupying lesion in the orbit, surgical removal was attempted. The orbit was opened by a Berke modification of the Krönlein operation and a cyst was exposed. During the dissection, the sac wall was perforated and the contents were evacuated. The sac wall was then painted with methylene blue to facilitate identification as it was excised. (3 figures, 2 references)

James W. Brennan.

Djacos, C. and Taptas, J. N. **A case of meningioma of the orbit.** Arch. d'opht. 20:171-175, March, 1960.

Meningiomas of the orbit, whether primary or secondary, are rare tumors and in Offret's review, published in 1951, only 162 cases could be collected from the literature. The authors report the case of a 60-year-old woman with exophthalmos and loss of vision, left eye. The lesion had been developing slowly for three years. The exophthalmos was irreducible and eye movements were restricted in all directions. Radiography revealed a marked opacification of the sphenoid sinus with hyperostosis involving the sphenoidal fissure. The optic canal was enlarged. The meningioma had been intracranial, with extension probably through the optic canal to the orbit. Surgery was refused by the patient. The article is illustrated by a clinical photograph of the exophthalmos and five reproductions of X-ray films of the orbit and cranium. (7 figures)

P. Thygeson.

Hartmann, K. **Post-operative treatment after orbital exenteration for carcinoma of the orbit.** Klin. Monatsbl. f. Augenh. 136:684-687, 1960.

Excellent epithelization of the orbit and uncomplicated healing within three

weeks were observed after post-operative topical treatment with aristamid gel (Nordmark). (3 figures, 16 references.)

Gunter K. von Noorden.

Jezegabel, C. **Ocular manifestations of pneumo-sinus dilatans. Clinical and etio-pathogenic study.** Arch. d'opht. 20:28-48, Jan-Feb., 1960.

The author reviews the literature on this rare disease, namely pneumo-sinus dilatans, and analyzes the 25 cases, chiefly in young people, that have been reported in the literature since Benjamin's initial observation in 1918. In their own case, in a boy of 14 years, there was a progressive and nonpainful protrusion of the right eye without visual disturbance. Radiography revealed a dilatation of the ethmoidal cells and frontal sinus on the affected side and normal maxillary sinuses. Surgical exploration showed osseous involvement only, with normal mucous membranes. The differential diagnosis from mucocele, tumor, and other conditions producing exophthalmos, is considered in detail and theories as to etiology are discussed. The author considers embryologic mesenchymal malformation as the most likely explanation. (3 figures, 29 references) P. Thygeson.

Mortada, A., and El-Toraei, I. **Orbital meningo-encephalcoele and exophthalmos.** Brit. J. Ophth. 44:309-314, May, 1960.

The congenital defect of communication between the brain and the orbit is rare but may occur as a herniation of brain tissue or simply a minute dural cyst. It may be anterior and located between the frontal, lacrimal, cribriform and maxillary bones or posterior within a natural opening, the optic foramen. The condition is present at birth and is usually accompanied by a pulsating proptosis which is usually progressive. The eye is usually displaced downward and outward. Diagnosis is made by X-ray study or by aspiration of

cerebrospinal fluid from the cyst. The treatment is often very difficult and is best done by means of a transfrontal approach; bone grafts are often necessary.

The authors describe the case of an 18-months-old infant which had an orbital meningo-encephalocoele which was apparently completely cured by surgical repair. (4 figures, 33 references)

Morris Kaplan.

Rosselet, E. **A case of exophthalmos associated with glaucoma.** Ophthalmologica 139:275-278, March-April, 1960.

A 76-year-old male patient with cardiovascular hypertensive disease developed at first a unilateral partial third nerve palsy, followed, three months later, by a rapidly increasing exophthalmos on the same side, associated with ocular hypertension. The impression was that of a pseudotumor of the orbit. On X-ray therapy the exophthalmos subsided promptly and completely, but the ocular hypertension persisted and resulted in serious visual damage. The patient's poor general condition made further investigation or surgical treatment of the glaucoma inadvisable. (10 references)

Peter C. Kronfeld.

15

EYELIDS, LACRIMAL APPARATUS

Charamis, J. and Topalis, C. **The use of alpha-chymotrypsin in lesions of the lacrimal passages.** Ann. d'ocul. 193:687-589, July, 1960.

Nineteen cases of disease of the lacrimal passages are presented in which alpha-chymotrypsin was used as an irrigating solution. These were of varying severity, one of which had a complete obstruction. In all cases repeated irrigations with alpha-chymotrypsin restored the patency of the lacrimal passages. David Shoch.

Gimenez Ruiz, Rafael. **Nephritis caused by an old purulent dacryocystitis.** Arch.

Soc. oftal. hispano-am. 20:327-328, April, 1960.

Acute nephritis developed in a 58-year-old man during an acute exacerbation of a chronic purulent dacryocystitis. Dilatation and drainage of the lacrimal sac was promptly followed by an improvement in the patient's renal and general condition.

Ray K. Daily.

deHass, E. B. H. **Lacrimal gland response to parasympathicomimetics after parasympathetic denervation.** A.M.A. Arch. Ophth. 64:34-43, July, 1960.

These reactions were studied in man after surgical interruption of the facial nerve above the geniculate ganglion in treatment of central nervous system tumors. The gland proved to be sensitized to direct parasympathomimetic agents administered subcutaneously. (3 tables, 8 references)

Edward U. Murphy.

Ruiz Barranco, F. and Velarde Canuelo, Y. M. **A case of malignant tumor of the lacrimal sac.** Arch. Soc. oftal. hispano-am. 20:154-159, Feb., 1960.

A man, 62-years-old, who for four years had recurrent attacks of acute left dacryocystitis which was controlled by penicillin, developed a neoplasm over the sac which proved to be a carcinoma. It rapidly invaded the nasal fossa and the preauricular gland. While the local neoplasm responded spectacularly to radiation and nitrogen mustard therapy, the patient subsequently died of pulmonary metastasis. The development of a malignancy in the site of a chronic inflammatory process makes the diagnosis difficult. The author suggests that every case of dacryocystitis with thickened walls be submitted to biopsy. (2 figures, 3 references)

Ray K. Daily.

Thiel, H. L. **Experiences with the operation after Toti.** Klin. Monatsbl. f. Augenh. 136:673-678, 1960.

The development of surgery of the tear system is reviewed. Dacryocystorhinostomy is preferred over simple extirpation of the tear sac. The latter procedure is indicated only in cases of lues, tumor of the sac, or lupus nasalis. The procedure used by the author is described. 159 out of 169 patients operated upon with a modified Toti technique were cured; i.e. the surgically created communication between tear sac and nose remained patent. The causes for surgical failures are mentioned. (4 figures, 22 references)

Gunter K. von Noorden.

Vedmedenko, A. I. and Kholodii, P. I. **Allergic dermatitis following the use of cortison.** Vestnik oftal. 4:37-38, July-Aug., 1959.

A patient with subsiding acute conjunctivitis was treated with instillation into the eyes of a suspension of cortisone. Two hours later an allergic dermatitis of the skin of the lids and face appeared, subsiding within a few days. (3 references)

Victor Goodside.

Wagner, H. J. **Experiences with the surgical procedure after Fox in entropion.** Klin. Monatsbl. f. Augenh. 136:688-691, 1960.

The causes leading to senile entropion and the surgical approach as described by Fox are reviewed. The simplicity of the procedure, as well as the excellent results achieved by the author with this technique make this operation the therapy of choice. (4 figures, 6 references)

Gunter K. von Noorden.

Zettl, W. **Further report on the advances of therapy in dacryocystitis.** Klin. Monatsbl. f. Augenh. 136:691-693, 1960.

Topical therapy with Combison ophthalmic ointment (a prednisolone-neomycin combination) has been found to yield good results. A lacrimal canula can be fitted directly to the tube and thus the

drug can be introduced easily into the lacrimal system. (1 figure)

Gunter K. von Noorden.

16

TUMORS

Harger, Robert. **Ocular tumors in children.** *Indiana St. M. A. J.* 53:662-670, April, 1960.

This is a review article prepared for the general practitioner. "Most of (the) remarks taken in condensed form directly out of our best existing texts," that is, Reese and Duke-Elder. It is a satisfactory compilation; no new material is presented.

Lawrence T. Post.

Nikolowski, W. and Seitz, R. **Cutaneous epithelioma (type Malherbe) adjacent to the globe.** *Klin. Monatsbl. f. Augenh.* 136:825-836, 1960.

The histologic characteristics of this benign tumor are discussed on the basis of three clinical observations. The tumor occurred in the palpebral area of children. Atheroma, hemangioma, and chalazion must be considered in the differential diagnosis. (14 figures, 20 references)

Gunter K. von Noorden.

Noguchi, T. T. and Lonser, E. R. **Oncocytoma (oxyphil-cell adenoma) of the caruncle of the eyelid.** *A.M.A. Arch. Path.* 69:516-519, May, 1960.

The article consists of a case report with biopsy findings of a tumor of the caruncle, occurring in a 63-year-old woman. The finding of typical, large cells, with abundant, finely granulated, acidophilic staining cytoplasm, and relatively small, central nuclei, was consistent with the diagnosis of oncocytoma (onkos = mass, bulk). This tumor, believed to be a derivative of ductal epithelium, occurs most commonly in the parotid gland, but also in any salivary gland, in glands of the pharynx, trachea, and esophagus, in

the thyroid and pituitary glands, and in the testis, Fallopian tubes, pancreas, liver, and stomach. In the caruncle it is postulated by the authors to have arisen from a sweat gland or from abortive lacrimal gland tissue, known to occur not infrequently in this location.

Lawrence T. Post.

Orban, T. **Tumor-like glial hyperplasia on the disc in a case of partly necrotic malignant melanoma.** *Ophthalmologica* 139:401-408, May, 1960.

The clinical examination of the painful blind left eye of this 62-year-old female patient revealed a beginning phthisis bulbi after chronic uveitis, possibly secondary to a very gross retinal detachment, the cause of which could not be determined by clinical means.

The histologic examination revealed a partly necrotic malignant melanoma which apparently had arisen close to the disc and had stimulated a tumor-like hyperplasia of the glial tissue of the disc. (3 figures, 14 references)

Peter C. Kronfeld.

Renard, G., Payrau, P. and Dhermy, P. **Cystic adenomas of the glands of Moll.** *Arch. d'opht.* 20:5-13, Jan.-Feb., 1960.

The authors note that sweat gland tumors have been described by dermatologists under the names "hydroadenoma" or "syringoma," but that little has been said of their localization in the glands of Moll. Two series of observations are reported and are beautifully documented by color plates of the histopathologic findings and of the clinical picture. The authors stress the interpalpebral location of the cystic tumors and the fact that they are frequently pigmented, necessitating their differential diagnosis from melanomas. They stress the need for histopathologic examination of these tumors on removal. (2 colored plates, 31 references)

P. Thygeson.

Smith, V. H., and Nicol, A. **Choroidal melanoma invading the orbit without distant metastases.** *Brit. J. Ophth.* 44:378-380, June, 1960.

A case of choroidal melanoma which had invaded the retrobulbar tissues is reported. The patient died as a result of another cause. Extensive micro- and macroscopic examination failed to reveal any evidence of metastases. (1 reference)

Irwin E. Gaynor.

Vit, H. **A case of advanced carcinoma terebrans.** *Klin. Monatsbl. f. Augenh.* 136: 682-684, 1960.

A report is given on an unusually extensive and progressive form of basal cell carcinoma of the face in a 71-year-old female patient. (1 figure, 2 references)

Gunter K. von Noorden.

Winter, F. C. and Kleh, T. R. **Precancerous epithelioma of the limbus.** *A.M.A. Arch. Ophth.* 64:208-215, Aug., 1960.

This all-inclusive term is proposed to replace such names as Bowen's disease, leukoplakia, dyskeratosis, and carcinoma-in-situ. The authors studied 24 cases clinically and histologically. All were treated by excision and there was recurrence in about a third, emphasizing the need for continued observation. (5 figures, 1 table, 30 references)

Edward U. Murphy.

17

INJURIES

Horns, R. C. **Injuries to the eye and visual apparatus associated with injury to the head, neck, and chest.** *Minnesota Med.* 43:314-320, May, 1960.

A general discussion of lacerations and contusions of the globe and adnexa is followed by a discussion of the ophthalmologic findings associated with head injuries. Prepared for the general practitioner, the article is an adequate review making free use of statistics presented in

papers by Blakeslee, Hooper, and Turner. No new material is offered.

Lawrence T. Post.

McCulloch, C. **Amaurosis after occlusion of internal carotid artery, treated by cyclodiathermy.** *Brit. J. Ophth.* 44:306-308, May, 1960.

A 50-year-old man received a heavy blow on the right side of the head; this was followed within a few days by partial paralysis of the left side and diminution of vision in the right eye. He also developed a low-grade glaucoma of the right eye. An arteriogram revealed a thrombus obstructing the right internal carotid artery which was removed by surgery. The vision continued to decrease to recognition of hand movements and there was also an increase in tension. A cyclodiathermy was done with improvement of vision to 20/50 and tension of 9.

The loss of vision was ascribed to the lowering of capillary blood pressure in the retina caused by the internal carotid obstruction and it was made worse by the glaucoma. The successful outcome of the surgery indicated that the nourishment of the retina does depend on a satisfactory balance between the retinal capillaries and the intraocular pressure. (2 references)

Morris Kaplan.

Vergez, A. **Usefulness of anterior chamber puncture in extraction of intraocular metallic foreign bodies.** *Ann. d'ocul.* 193: 708-709, Aug., 1960.

The author states that in removing an intra-ocular foreign body, a useful sign is a slight bulging of the sclera when the magnet is placed over the foreign body. He feels that this bulging is more easily seen in a hypotonic eye. Therefore, in order to render the eye hypotonic, he performs a puncture of the anterior chamber. This is done before an incision is made in the sclera to remove the foreign body.

David Shoch.

18

SYSTEMIC DISEASE AND PARASITES

Camino, C. and Correa, E. **Pulseless disease.** Arch. chil. de oftal. 16:131-137, July-Dec., 1959.

The authors describe a case of pulseless disease which had beginning eye symptoms of amaurosis fugax which lasted for only a few seconds. However, these episodes become more frequent and longer-lasting until finally a complete blindness occurred. It is noteworthy that this patient was seen for the first time about one year before the diagnosis was made; she had a history of episodes of amaurosis fugax and nothing was found in her physical examination. By the time she returned, one of her eyes was totally blind with a dilated, non-reactive pupil and she was beginning to have symptoms in her other eye. Only after hospitalization and a routine general physical examination was it found that the patient did not have a radial pulse, which made the diagnosis possible. The surgical procedure which is being used in an attempt to cure this otherwise fatal disease is briefly discussed. (1 figure, 3 references)

Walter Mayer.

Denko, C. W. and Bergenstal, D. M. **The sicca syndrome (Sjögren's syndrome): a study of sixteen cases.** A.M.A. Arch. Int. Med. 105:849-858, June, 1960.

The diagnosis was made by a combination of 1. evidence of parotid, nasal, or lacrimal gland hypofunction, and 2. some symptom of joint involvement, such as pain, stiffness, swelling, capsular thickening, redness, or heat. Less frequently the patients thus diagnosed exhibited fatigue, muscular weakness, parotid swelling, pigment changes, atrophy of muscles, and weight loss. Half of the patients showed frank rheumatoid arthritis. Blood studies revealed high gamma-globulin, C-reactive

protein, and cryoglobulin levels. Lymphocytic infiltration, atrophy, and fibrosis characterized biopsies of the parotid gland. As regards etiology, the varied symptomatology and the blood picture suggest to the authors some form of allergy. They recommend a combination of prednisone and one to two grains of thyroid daily as the best therapy for both the joint symptoms and the dryness.

Lawrence T. Post.

Dowling, J. L. and Smith T. R. **An ocular study of pulseless disease.** A.M.A. Arch. Ophth. 64:236-243, Aug., 1960.

A case of this condition, also known as the aortic arch syndrome, was examined clinically and pathologically. Multiple microaneurysms, irregularly dilated veins with segmented blood flow, and decreased central retinal artery pressures were found. There was a striking absence of retinal hemorrhages and exudates. (9 figures, 20 references)

Edward U. Murphy.

Hales, I. B. and Rundle, F. F. **Ocular changes in Graves' disease.** Quart. J. Med. 29:113-126, Jan., 1960.

What is a patient with Graves' disease going to look like in 15 years as far as his eyes are concerned? The authors have attempted to discover this by examining 104 patients whose symptoms and signs had been recorded by them approximately 15 years previously.

Of the 104 patients, 64 were euthyroid at the time of their first examination (most of them from having already been treated); 40 were hyperthyroid awaiting surgery, and of these only 19 had eye signs. Hence, the reversion on treatment from the hyperthyroid to the euthyroid status could have influenced the comparison in only these 19 cases. Various forms of treatment were employed, either before or after the initial examination (thyroid-

ectomy, 89; anti-thyroid drugs, 7; radio-active iodine, 1; long term thyroid treatment, 7). The status of the 104 patients after 15 years may be tabulated as follows:

Thyroid status:

Hyperthyroid, none

Euthyroid, 93

Hypothyroid, 11

Exophthalmus (2 mm. or more change):

Decreased, 5

Unchanged, 75

Increased, 24

Considerably, 7

Severely, and only after treatment, 1

Ophthalmoplegia:

Unchanged, 2/3

Normal previously, with interval development of pareses, 6

"Paralytic squint," on first examination, 8

Recovery on second examination, 4

Unchanged, 4

Lid retraction (of those affected):

Return to normal, 60 percent

Generally decreased, 40 percent

Separation of lids in sleep; 17 cases:

Complete recovery, 14

Lawrence T. Post.

Hamilton, H. E., Schultz, R. O. and De Gowin, E. L. **The endocrine eye lesion in hyperthyroidism: its incidence and course in 165 patients treated for thyrotoxicosis with Iodine-131.** A.M.A. Arch. Int. Med. 103:675-685, May, 1960.

The average ophthalmologist views the treatment of his patients for thyrotoxicosis with considerable apprehension. However, most physicians do not know how often they must look for trouble. This study should provide a guide to short term prognosis. The paper records the course of the eye signs and symptoms of 165 patients, after the return to normal of the BMR on treatment with radio-active iodine.

Eye signs or symptoms were present in three-quarters of the 165 thyrotoxic patients. Of these one-half were minimal, one-third moderate, and one-sixth severe. After normalization of the BMR, one-half of the latter patients no longer had eye signs or symptoms. Of the half who continued to show signs or symptoms, only one-fourth had significant ones.

The eye changes are divided into four categories: 1. exophthalmus (the only change which alone is not symptomatic), 2. lid retraction, 3. extra-ocular muscle pareses, and 4. tissue reaction: congestion and edema (producing the most distressing symptoms, i.e., pain, pressure, burning, diplopia, and diminished vision). Symptomatically, the vast majority of the patients showed marked improvement, even in the face of increasing proptosis. However, during treatment, the symptoms of nine patients became temporarily worse, and, after treatment, during maintenance of the euthyroid state, the symptoms of seven progressed for the worse.

As for signs, the proptosis in two-thirds of the 160 patients with this abnormality became worse, while in one-third it improved.

A rapid response to treatment uniformly caused less aggravation of eye signs and symptoms and was followed by fewer residuals. A secondary hypothyroidism was associated with no greater eye changes than was a normal BMR. No way was deduced to predict the response of an individual patient to therapy, and no consistent sub-classifications of Graves' disease could be arrived at.

Lawrence T. Post.

Van Leeuwen, Gerard and Brooke, C. E. **Oculoglandular cat-scratch disease.** A.M.A. J. Dis. Child. 99:667-668, May, 1960.

This is the seventeenth case report in the American literature of a typical Par-

inaud's syndrome caused by cat-scratch disease, in this instance, affecting an 11-year-old, white girl. The diagnosis was confirmed by skin testing with cat-scratch antigen. The authors believe that this now well-known disease, for which no organism has as yet been found, is commoner than is generally realized. They emphasize the benign but occasionally protracted course. Lawrence T. Post.

19

CONGENITAL DEFORMITIES, HEREDITY

Busch, G., Weiskopf, J. and Busch, K.-T. **Dysgenesis mesodermalis et ectodermalis Rieger, or Rieger's disease.** Klin. Monatsbl. f. Augenh. 136:563-568, 1960.

This is the report of a family in which congenital malformations of iris, chamber angle, cornea, and teeth combined with myotonic dystrophy were observed in male and female members through five generations. Mesodermal as well as ectodermal structures are involved in this syndrome. (8 figures, 62 references)

Gunter K. von Noorden.

Gärtner, J. **Equatorial degenerations of non-myopic patients in status dysrhabdus and neuro-cutaneous dysplasia.** Klin. Monatsbl. f. Augenh. 136:620-635, 1960.

Observations made in two families indicate that equatorial retinal degenerations in non-myopic eyes belong to the group of hereditary ocular diseases. The retinal degenerations described are associated with unspecific signs of other hereditary manifestations such as status dysrhabdus and pigmentary skin anomalies. In view of the extraocular findings the author surmises that equatorial degenerations are part of a developmental anomaly involving other body structures as well. An ophthalmoscopic examination is, therefore, indicated in patients with status dysrhabdus, syringomyelia and neuro-cutaneous dysplasias. (4 figures, 20 references) Gunter K. von Noorden.

Heidensleben, E. **Poikiloderma congenitale accompanied by megalocornea in one eye.** Acta opth. 38:280-284, 1960.

Microphthalmus and coloboma have been previously reported together with poikiloderma. The present case with unilateral microphthalmus reinforces the possibility of poikiloderma being an ectodermal and mesodermal dysplasia. Rothmund's and Thomsen's syndromes may be manifestations of the same condition. (2 figures, 11 references) John J. Stern.

20

HYGIENE, SOCIOLOGY, EDUCATION, AND HISTORY

Gormaz, A. and Eggers, C. **Eye banks.** Arch. chil. de oftal. 16:47-53, Jan.-June, 1959.

The authors describe their method for setting up an Eye Bank in Chile and the methods they have used to store donor material, as well as their criteria for acceptance or refusal of donor eyes. They preserve the corneas in vaseline. It may be interesting to point out that while they refuse eyes with a positive bacterial growth, they also have seen some eyes which, while being preserved, become totally opaque within two days and they speculate as to what would have happened if these eyes had been used immediately for a kertosplasty. (2 tables, 13 references) Walter Mayer.

Lijo Pavia, J. **Relationship between ophthalmology and otology.** Rev. otoneuro-oftal. Sudam. 34:59-67, Oct.-Dec., 1959.

This paper deals in great detail with all the different otologic and neurologic problems which are the common field of the otologist and of the ophthalmologist. The author describes the different diseases in this category without discussing problems of therapeutics.

Walter Mayer.

NEWS ITEMS

EDITED BY DONALD J. LYLE, M.D.

411 Oak Street, Cincinnati 19, Ohio

News items should reach the editor by the 10th of the month. For adequate publicity, notice of postgraduate courses and meetings should be received three months in advance.

DEATHS

Dr. Ralph Aranovitz Arnold, Durham, North Carolina, died July 17, 1960, aged 49 years.

Dr. Hendrie Walter Grant, Saint Paul, Minnesota, died August 5, 1960, aged 66 years.

Dr. George Martin McBean, Chicago, Illinois, died August 27, 1960, aged 85 years.

Dr. Lloyd Mills, Rancho Santa Fe, California, died August 12, 1960, aged 80 years.

ANNOUNCEMENTS

RESEARCH STUDY CLUB

Guest speakers in ophthalmology for the 30th annual midwinter convention in ophthalmology and otolaryngology of the Research Study Club of Los Angeles will be Dr. Med. Gerd Meyer-Schwickerath, professor of ophthalmology, University of Bonn, Essen, Germany, Dr. Lorenz E. Zimmerman, Armed Forces Institute of Pathology, Washington, D.C., Dr. Juan Heatley, professor of ophthalmology, School of Medicine, National University of Mexico, Mexico City, Dr. Robert L. Tour, San Francisco, Dr. Robert E. Christensen and Dr. Robert J. Schilling, Los Angeles.

Registration is on January 22, 1960, and meetings are from January 23rd through January 27th. In order to be eligible for attendance at the convention, all applicants must be members in good standing of the American Medical Association. The fee for the course or any part of it is \$110.00 and includes the cost of all round-table luncheons. Checks, made payable to the Research Study Club, should be mailed to Norman Jesberg, M.D., treasurer, 500 South Lucas Avenue, Los Angeles 17, California.

FLORIDA MIDWINTER SEMINAR

The 15th annual Florida Midwinter Seminar in ophthalmology and otolaryngology will convene January 29, 1961, and continue through February 4th, at the Americana Hotel, 9701 Collins Avenue, Miami Beach, Florida. The lecturers on ophthalmology on January 30th and 31st and February 1st, will be Walter S. Atkinson, Watertown, New York; William Havener, Columbus, Ohio; Charles E. Iliff, Baltimore; Irving Leopold, Philadelphia; and A. Edward Maumenee, Baltimore.

The registration fee for the seminar is \$50.00. A check for \$10.00 payable to the Florida Midwinter Seminar must accompany the application. This is not returnable. The remainder of the registration fee will be paid at the Seminar desk at the Americana Hotel on arrival. All the facilities of the Americana, including the beach and swimming pool, are available to all the registrants of the Seminar and their families. The hotel will also provide free transportation to the Westview Country Club for those desiring to play golf. For further information write

to Dr. Kenneth Whitmer, 550 Brickell Avenue, Miami, Florida.

WASHINGTON HOSPITAL LECTURES

The Saturday morning lectures of the Department of Ophthalmology, Washington Hospital Center, Washington, D.C., scheduled for February are: February 4th, "Refraction," Dr. James B. Bain and Dr. Everett S. Caldemeyer; February 11th, "Refraction," Dr. James B. Bain; February 18th, "Refraction," Dr. Ben S. Fine, and "Visual aids," Dr. Everett S. Caldemeyer; February 25th, "Opticianry," Guild opticians, and "Panel on refraction problems," Drs. Bain, Gurwin and Caldemeyer.

EASTERN SECTION

The 1961 meeting of the Eastern Section of the Association for Research in Ophthalmology will be held in the 14th floor Assembly Hall of the Clinical Center at the National Institutes of Health, Bethesda, Maryland. The registration will be at 8:45 a.m., February 17th, in the lobby outside the hall. The time for each presentation at the section meeting is limited to 15 minutes and five minutes will be held for discussion.

Abstracts should be sent to the local chairman, Dr. Ludwig von Sallmann, National Institute of Neurological Diseases and Blindness, Bethesda 14, Maryland. Arrangements have been made for luncheon in the cafeteria of the Clinical Center and there will be a subscription dinner at the Navy Officers Club, Friday evening.

TORONTO COURSE

The Division of Postgraduate Medical Education, Faculty of Medicine, University of Toronto, announces that an eye surgery clinical meeting has been arranged by the Department of Ophthalmology for Monday, Tuesday and Wednesday, March 20, 21 and 22, 1961. Two outstanding eye surgeons will be the guest speakers: Sir Benjamin Rycroft, F.R.C.S., London, England, and Dr. Robert N. Shaffer, San Francisco. Surgical clinics will be held in the university teaching hospitals in the mornings with symposia and lectures in the afternoons. The guest surgeons will take part in symposia on cataract surgery, keratoplasty and children's eye diseases. In addition to the guest lecturers, the staff in the Department of Ophthalmology in the University will participate. Registrants are cordially invited to attend the Departmental Research Meeting on Saturday, March 18th. The guest of honor will be Dr. Hermann Burian, professor of ophthalmology, University of Iowa, and an authority on orthoptics. The fee is \$50.00 (Canadian funds).

GILL MEETING

The Gill Memorial Eye, Ear and Throat Hospital, Roanoke, Virginia, will hold its 34th annual

spring congress in ophthalmology and otolaryngology and allied specialties, April 10 through April 15, 1961. There will be 20 guest speakers and 50 lectures.

NEW YORK EYE AND EAR MEETING

The annual spring meeting of the Alumni Association of the New York Eye and Ear Infirmary will be held April 17 through 20, 1961.

The entire meeting will be oriented toward glaucoma. Symposia will be offered on diagnostic work-up, medical management and surgical management. Courses will also be given on related subjects and a closed-circuit television demonstration of surgical procedures will be held.

Additional information may be obtained by writing to: Dr. John R. Finlay, secretary, Alumni Association, 218 Second Avenue, New York 3, New York.

INSTITUTO BARRAQUER COURSE

The III International Course in Ophthalmology of the Instituto Barraquer will be held from May 1 to 5, 1961, in Barcelona at the Avenida Palace Hotel, Avenida José Antonio, 605, with the collaboration of the following lecturers: Hermenegildo Arruga, Alfred Bangerter, Conrad Berens, Henri Begue, C. D. Binkhorst, Jørn Boberg-Ans, José Casanovas, Ramón Castroviejo, P. M. Caudell, Ivo Correa-Meyer, Emilio Diaz Caneja, Werther Duque Estrada, R. M. Fasanella, Olga Ferrer, A. Franceschetti, Louis Girard, Alfred Huber, Herbert M. Katzin, John Harry King, Jules Legrand, Luigi Maggioro, Frank W. Newell, Louis Paufigue, Paul Payrau, Antonio Piñero, Hans Remky, Cyro de Rezende, Harold Ridley, Michael John Roper-Hall, Alejandro Salleras, Giuseppe Scuderi, C. D. Shapland, Byron Smith, Benedetto Strampelli, Saul Sugar, Chr. Topalis and others.

The scientific program will include a symposium on the "Surgery of the lens," and a symposium on "Surgery of the cornea." A service for simultaneous translation from and into the official languages of the course (Spanish, French and English) is provided for the scientific sessions. Registration will open on January 15, 1961, and is limited to 300 ophthalmologists. Address the Secretary, Instituto Barraquer, Laforja 88, Barcelona, Spain.

BRITISH OPHTHALMIC TRADE FAIR

The largest ophthalmic trade fair ever to be held in Europe will take place from July 4 through 7, 1961, in London. Further information may be obtained by writing Ophthalmic Exhibitions, Ltd., Columbia House, 69 Aldwych, London, W.C. 2.

MISCELLANEOUS

SOUTHERN MEDICAL ASSOCIATION

Chairman of the Section on Ophthalmology and Otolaryngology of the Southern Medical Association which met in Saint Louis recently is Dr. George M. Haik, New Orleans. On the ophthalmic program were: "Preventive and curative treatment of retinal detachment: Surgical demonstrations," Paul A. Cibis and Bernard Becker, Saint Louis;

"Closure of corneal wounds with catgut sutures," Samuel D. McPherson, Jr., Durham, North Carolina; "Acquired strabismus in adults," James E. Miller, Saint Louis; "Glaucoma family study," Allan E. Kolker and Robert A. Moses, Saint Louis; "Subluxated and dislocated lenses," George M. Haik; "A clinical study of alternating hypertropia," A. D. Ruedeman, Jr., Detroit; "Iatrogenic eye diseases," William W. Voolton, Charleston, South Carolina.

"Effect of whiplash injuries on ocular functions," Harry Horwich and David Kosner, Coral Gables, Florida; "Alpha chymotrypsin in cataract surgery: Contraindications and complications," Alston Callahan, Birmingham, Alabama; "Light coagulation in treatment of retinal diseases," John F. Nowell and George S. Ellis, New Orleans; "Therapy of cephalosporium keratomycosis," Wendell D. Gingrich, Galveston, Texas; "Congenital cataracts," Clay W. Evatt, Milton Adler and Elsie Taber, Charleston, South Carolina; "Useful variations in techniques for surgery of blepharoptosis," Robert A. Schimek, New Orleans. A symposium on "Contact lenses" was presided over by Thomas J. Vanzant, Houston, with Donald Fonda, Ridgewood, New Jersey, and Jack Lee, San Antonio, Texas, as panel members.

MIDWINTER RESEARCH MEETING

The program for the midwinter meeting of the Association for Research in Ophthalmology, Inc., at the Roosevelt Hotel, New Orleans, Louisiana, December 5th, 6th and 7th included:

"Studies on the membrane properties of ciliary epithelium in coldblooded vertebrates," Julia T. Apter, M.D., Chicago; "Short circuit current and resistance of the in vitro iris-ciliary body membrane preparation," Monte G. Holland, M.D., Dallas Mallerich, Bruce Tischler, B.S., and Joseph Bellestri, B.S., New Orleans; "Pressure cup techniques for the measurement of aqueous humor formation in human subjects," M. E. Langham, Ph.D., Baltimore; "Regulatory changes in intraocular dynamics evoked by tonometry and tonography," Mansour F. Armaly, M.D., Iowa City; "The effect of hypothermia on aqueous humor dynamics: III. Turnover of ascorbate and sodium," Bernard Becker, M.D., Saint Louis; "The effect of hypothermia on aqueous humor dynamics: IV. Carotid artery ligation and blood flow," Irvin P. Pollack, M.D., and Bernard Becker, M.D., Saint Louis.

"A plasma-mannitol-brom cresol purple agar for rapid identification of staphylococci," Robert P. Burns, M.D., and Mary Jo Florey, B.S., Portland, Oregon; "Cataracts induced by maternal hypersensitivity in mice," Aleta Nichols Barber, Ph.D., James Willis, M.D., and Charles Afeman, M.D., New Orleans; "The experimental production of granulomas of the iris by pine pollen in hypersensitized guinea pigs," Stan Coleman, M.D., Saint Louis; "The homo-immune uveitides in the guinea pig," Samuel B. Aronson, M.D., Phyllis Zweigert, and Michael J. Hogan, M.D., San Francisco; "Tissue culture studies of toxoplasma," Michael J. Hogan, M.D., Chieko Yoneda, M.D., and Phyllis Zweigert, A.B., San Francisco; "Effect of corticosteroid hormone on herpes simplex keratitis," Samuel J.

Kimura, M.D., and Michael J. Hogan, M.D., of San Francisco.

"The nature of contrast phenomena," Milton Flocks, M.D., Palo Alto, California; "Visualization of wave-guide modes in retinal receptors," Jay M. Enoch, Ph.D., Saint Louis; "Blurring retinal image on foveal contrast thresholds for different sizes of test objects," Kenneth N. Ogle, Ph.D., Rochester, Minnesota; "Receptor orientation in retinal pathology," Franz Frankhauser, M.D., Jay M. Enoch, Ph.D., and Paul A. Cibis, M.D., Saint Louis; "Desynchronization of the corneo-retinal potential of both eyes," Hansjorg Kolder, M.D., and Gerhard A. Brecher, M.D., Atlanta, Georgia; "Transconjunctival photocoagulation of ciliary body and retina with a new photocoagulator," James E. McDonald, M.D., and Rana P. Sinha, M.D., Chicago.

"Outflow resistance of the rabbit eye: Techniques and effects of acetazolamide," Marvin L. Sears, M.D., Baltimore; "The distribution in ocular and spinal fluids of dimethylxazolidine-2, 4 dione (DMO) and related compounds," Marguerite A. Constant, Ph.D., Saint Louis; "The transport of organic anions by the rabbit ciliary body: III. Measurement of rate of aqueous flow," Max Forbes, M.D., Saint Louis; "Studies on the corneal endothelium of the rabbit," Ludwig von Sallmann, M.D., and Leo L. Caravaggio, M.S., Bethesda, Maryland; "The effect of intralaminar plastic membranes on corneal physiology," William F. Knowles, M.D., New Orleans; "Studies on the transparency of preserved corneas," F. W. Stocker, M.D., M. Th. Matton-Van Leuven, M.D., A. Eiring, M.S., R. Georgiade, M.D., and N. Georgiade, M.D., Durham, North Carolina.

"The incorporation of labelled amino acids into lens proteins of normal galactose, and xylose fed rats," Sidney Lerman, M.D., Anima Devi, Ph.D., and Suzzan Hawes, B.A., Rochester, New York; "Cotton wool spots of the retina," J. Reimer Wolter, M.D., Ann Arbor; "Structure of the rabbit cornea: A study with silver stains," Frank M. Polack, M.D., New York; "Electron microscopy of the choroid: Cells and supporting structure," Lynette Feeney, A.B., and Michael J. Hogan, M.D., San Francisco; "Electron microscopy of the choroid: Blood vessels," Michael J. Hogan, M.D., and Lynette Feeney, A.B., San Francisco; "Electron microscopy of the choroid: The chorioidal nerves," Lynette Feeney, A.B., and Michael J. Hogan, M.D., San Francisco.

EMORY UNIVERSITY COURSE

The Department of Ophthalmology, Emory University School of Medicine, Atlanta, Georgia, presented a course on ophthalmic surgery at the Grady Memorial Hospital on December 1st and 2nd. Members of the faculty were Dr. Frank D. Costenbader, Washington, D.C., Dr. John M. McLean, New York, and Dr. Harold G. Scheie, Philadelphia.

CLEVELAND CLINIC

The Frank E. Butts Educational Institute affiliated with the Cleveland Clinic Foundation, Cleveland, Ohio, sponsored a course on "Newer developments in ophthalmology," at which the speakers

were Drs. Victor A. Byrnes, St. Petersburg, Florida, Charles D. Regan, Boston, C. Dwight Townes, Louisville, Kentucky, and Victor G. De Wolfe, Wallace B. Hamby, William A. Hawk, C. Robert Hughes, Roscoe J. Kennedy, Charles L. Leedham, James E. Nousek, Jr., and Charles A. Resch, all of Cleveland.

SOCIETIES

AMERICAN COLLEGE OF SURGEONS

On Monday, March 6, 1961, and Tuesday, March 7th, at the sectional meeting of the American College of Surgeons to be held in Philadelphia, the following program on ophthalmic surgery will be presented: Symposium on recent advances in ocular surgery—"Cataract extraction," John M. McLean, New York; "Retinal detachment surgery," Robert J. Brockhurst, Boston; "Glaucoma surgery," W. Banks Anderson, Durham; "Tumors of the eye and orbit," Algernon B. Reese, New York; "Corneal surgery," William F. Hughes, Chicago.

Symposium on pediatric ophthalmology—"Inheritance of defects," Harold F. Falls, Ann Arbor; "Chorioretinitis and iridocyclitis in children," John R. Fair, Augusta, Georgia; "Congenital cataracts," Frank D. Costenbader, Washington; "Congenital glaucoma," A. Edward Maumenee, Baltimore; "The etiology of strabismus," Francis Heed Adler, Philadelphia; "Surgery of strabismus," Trygve Gundersen, Boston.

GEORGIA SOCIETY

The Georgia Society of Ophthalmology and Otolaryngology will meet at the General Oglethorpe Hotel, Wilmington Island, Savannah, Georgia, on March 2, 3 and 4, 1961. The program for ophthalmology includes; "Management of the complications of cataract surgery," C. Dwight Townes, Louisville, Kentucky; "Tumors of the eye and adnexa in children," Charles E. Iliff, Baltimore; and "The management of intraocular malignancy," Edwin B. Dumphy, Boston.

UNITED KINGDOM

The annual congress of the Ophthalmological Society of the United Kingdom will be held at the Royal Society of Medicine, 1 Wimpole Street, London, W. 1, on April 13, 14 and 15, 1961. The president's address will be delivered by Mr. Frank W. Law. The subject for discussion will be "Neovascularization in ocular disease," with Prof. Norman Ashton and Mr. Redmond Smith acting as openers. Mr. A. J. B. Goldsmith and Mr. J. R. Hudson will be among the speakers at the symposium on "The late complications of aphakia." The 1961 Bowman Lecture will be delivered by Miss Ida Mann, Perth, Australia, whose subject will be "Climates, cultures and eye diseases."

PERSONAL

Dr. Dohrmann K. Pischel, Stanford University School of Medicine, delivered the XV. Francis I. Proctor Lecture at the University of California San Francisco Medical Center, on December 2nd. The subject of Dr. Pischel's Lecture was "Surgical treatment of retinal cysts."

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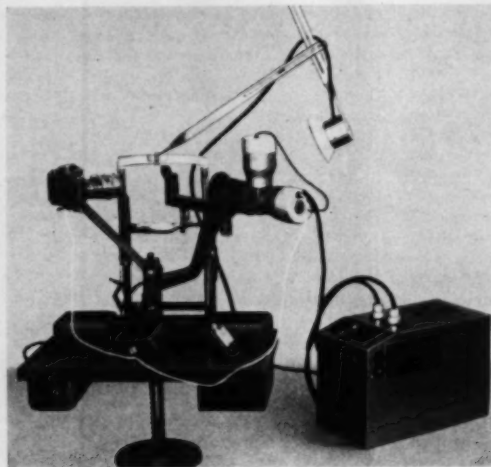
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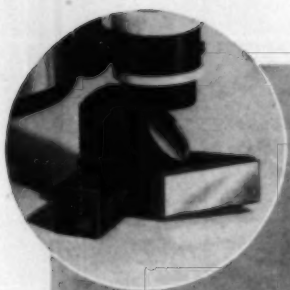
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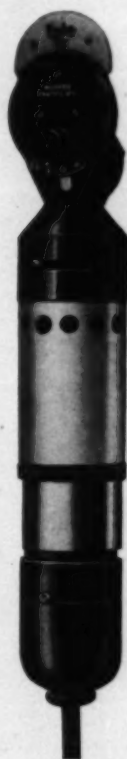
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